VOLUME 79 NUMBER 2

AMERICAN JOURNAL OF DISEASES OF CHILDREN

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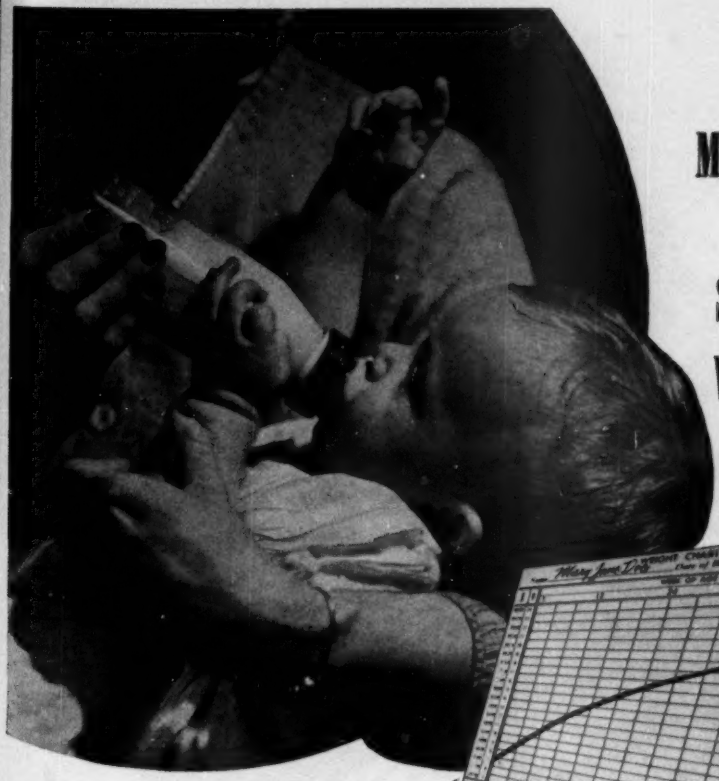

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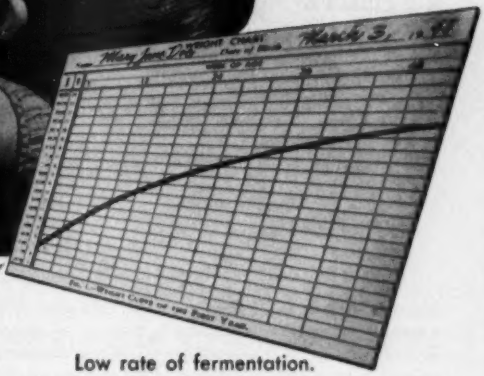

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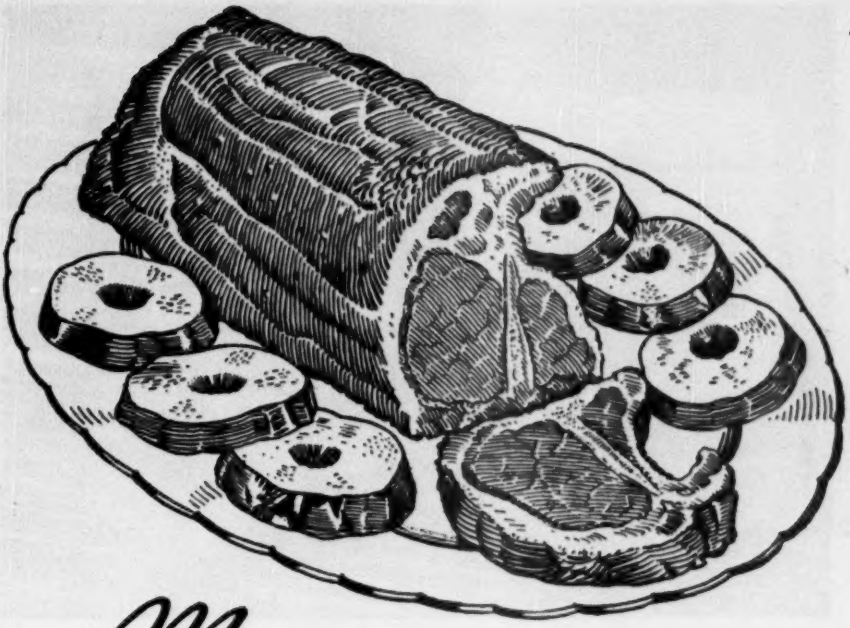

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*McLester, J. S.: Protein Comes Into Its Own, J.A.M.A. *139*:897 (Apr. 2,) 1949

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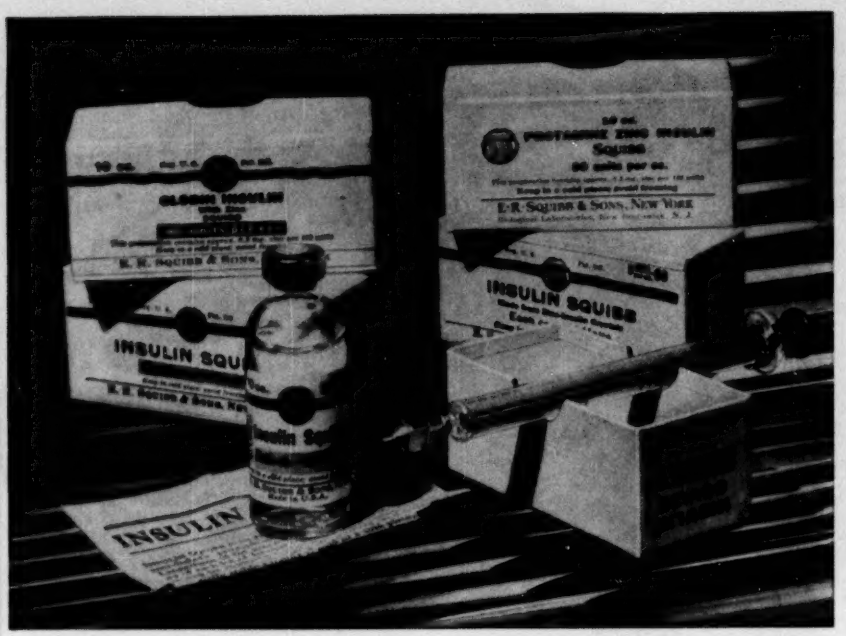

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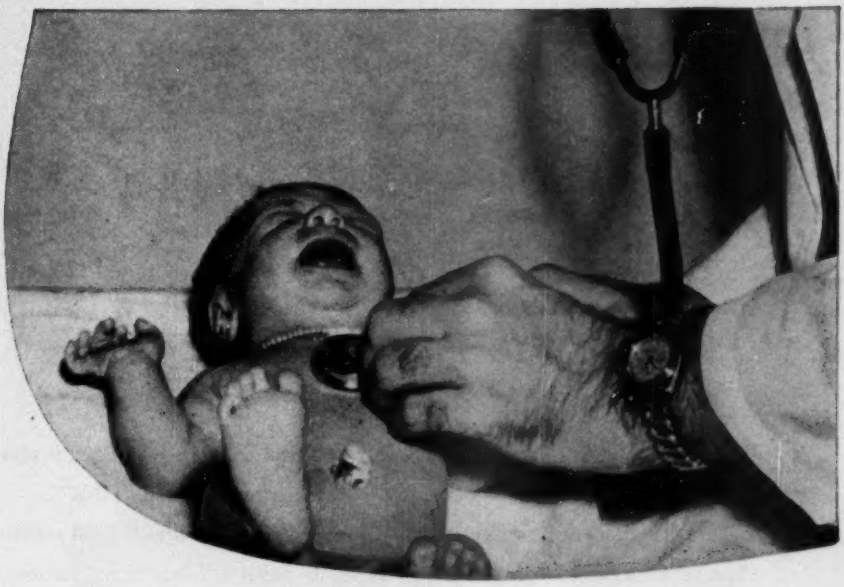

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References:

1. Jeans, P. C. and Marriott, W. M.: Infant Nutrition, Mosby, 4th ed., 1947.
2. McLester, J. S.: Nutrition and Diet, Saunders, 4th ed., 1944.
3. Rose, M. S.: Rose's Foundation of Nutrition, rev. by MacLeod and Taylor, Macmillan, 4th ed., 1944.
4. Sherman, H. C.: Chemistry of Food and Nutrition, Macmillan, 7th ed., 1946.

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American Journal of Diseases of Children

VOLUME 79 FEBRUARY 1950 NUMBER 2

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PREVALENCE OF RHEUMATIC HEART DISEASE AT HIGH ALTITUDES

BERNICE G. WEDUM, M.D.
WASHINGTON, D. C.

WARD DARLEY, M.D.
AND
PAUL H. RHODES, M.D.
With the assistance of Ella Jane Swan
DENVER

COLORADO has been among the first five states in deaths from rheumatic heart disease among school children for twenty years.[1] A preliminary examination of 1,845 Denver school children revealed a prevalence of 1.6 per cent, which is not unusual when compared with that of other areas.[2] One report has appeared suggesting that the prevalence of rheumatic heart disease increases with increasing altitudes.[3] Chavéz reported that there is a higher incidence of rheumatic heart disease among adults who die of heart disease in México, D. F., Mexico, where the altitude is 8,000 feet (2,438 meters), than anywhere else in the world.[4] The altitude in Denver is 5,183 feet (1,580 meters), but the altitude in Colorado ranges from 3,350 to 14,431 feet (1,021 to 4,399

This study was aided by a grant from the Life Insurance Medical Research Fund.

From the Denver Area Rheumatic Fever Diagnostic Service, University of Colorado Medical Center.

1. Hedley, O. F.: Trends, Geographical and Racial Distribution of Mortality from Heart Disease Among Persons Five to Twenty-Four Years of Age in the United States During Recent Years (1922-1936), Pub. Health Rep. **54**:2271 (Dec. 29) 1939. Calculated from United States Census of 1940 and United States Vital Statistics 1939-1942 for International List of Causes of Death: Numbers 58, 90a, 92b, 92c, 93c and 95b.

2. Wedum, B. G.; Wedum, A. G., and Beaghler, A. L.: Prevalence of Rheumatic Heart Disease in Denver School Children, Am. J. Pub. Health **35**:1271 (Dec.) 1945.

3. Sampson, J. J.; Hahman, P. T.; Halverson, W. L., and Shearer, M. C.: Incidence of Heart Disease and Rheumatic Fever in School Children in Three Climatically Different California Communities, Am. Heart J. **29**:178-204 (Feb.) 1945.

4. Chavéz, I., in discussion on Chavéz, I.; Sepúlveda B., and Ortega, A.: The Functional Value of the Liver in Heart Disease, J. A. M. A. **121**:1276 (April 17) 1943.

meters), with an approximate mean of 6,800 feet (2,073 meters). It seemed possible that the high death rate among children in Colorado might be a reflection of unusually high prevalence rates or unusually severe forms of rheumatic heart disease among children living at high altitudes. The present paper reports studies on a group of children living at an altitude of 10,000 feet (3,048 meters) or above.

METHODS

A total of 1,017 children living at an altitude of 10,000 feet or above was examined. There were 502 boys and 515 girls who were 5 to 23 years of age. All but 37 lived in Lake County, where the estimated population of school age (those persons aged 5 to 21 years) was 1,454.

Lake County is situated in a high valley surrounded by snow peaks. The winters are long and rigorous, though sunnier than those of mountain towns lying nearer seacoasts. The water supply is low in minerals and not thoroughly protected from contamination. The largest town, Leadville, has a population of 4,774 (census of 1940). Since there is no farming in such high valleys, the supply of meat, vegetables and pasteurized milk is variable. Mining and lumbering are the chief, almost the only, industries; thus, the proportion of laborers in the population is high.

A bed or a padded high table in a quiet room was provided for each physician. All children were examined supine with the chest bare, and the majority were examined in the left lateral position after exercise and again in the erect position with the breath held in expiration. Hemoglobin determinations (Sahli method) and sedimentation rates (Wintrobe uncorrected method) were done when these procedures seemed indicated clinically.

The examinations were carried out by persons who had worked together for a year in the Denver Area Rheumatic Fever Diagnostic Service and who were thoroughly familiar with rheumatic heart disease in children. Consultation was frequent, and in many cases a child was examined by all the physicians. The period spent with each child ranged from five to thirty minutes.

CLASSIFICATION OF CASES AND CRITERIA OF DIAGNOSIS

I. Rheumatic heart disease

A. Mitral insufficiency

This diagnosis was made in the presence of a faint to loud, high-pitched, blowing, sometimes harsh and shrill systolic murmur heard best with the diaphragm of a Rieger-Bowles stethoscope. The murmur is maximal at the apex and transmitted to the axilla, extending through almost all of systole. It is usually accentuated after exercise with the child in the left lateral position holding the breath in expiration. It should be noted that this murmur is never transmitted to the neck, that it is frequently more difficult to hear with the child erect and that rarely it is heard only late in systole. The presence or absence of a history of rheumatic fever did not influence the diagnosis. The quality of this murmur can be appreciated by listening with the bell of the stethoscope on the back of the hand while a finger is passed over the adjacent skin with a light touch.

B. Mitral stenosis

This condition was indicated by a faint to loud, low-pitched, rumbling mid-diastolic murmur with presystolic accentuation, heard best with the bell of a

Rieger-Bowles stethoscope at, or close to, the apex with the child in the left lateral position after exercise, holding the breath in expiration.

C. Aortic insufficiency.

A faint to loud, high-pitched, blowing diastolic murmur, usually heard best in the third left intercostal space with the patient leaning forward from the erect position and holding the breath in expiration, characterizes this lesion. This murmur is occasionally heard best at the apex and is also occasionally heard best with the child recumbent.

D. Aortic stenosis—rheumatic

The presence of this condition was detected by a harsh, blowing, systolic murmur, heard best over the aortic area, which is transmitted to the apex and neck and accompanied with a thrill over the aortic area and vessels of the neck, a low pulse pressure, a diminished aortic second sound and the murmur of aortic insufficiency.

E. Possible rheumatic heart disease

This diagnosis was made in the presence of:

(1) questionable apical systolic murmurs in a child with a history of rheumatic fever; (2) absent first heart sound; (3) a loud first sound and accentuated pulmonary second sound, especially when there was a record of an apical low-pitched diastolic murmur previously heard or a definite history of rheumatic fever.

II. Congenital heart disease

A. Patent ductus arteriosus

This malformation was diagnosed in the presence of a characteristic continuous systolic and diastolic murmur heard best over the second left intercostal space, with or without a thrill.

B. Interventricular septal defect

A loud, harsh, medium-pitched to low-pitched systolic murmur heard best over the third left intercostal space suggests the presence of this defect. The murmur extends about two thirds through systole and is transmitted toward the right side of the chest and toward the apex but not into the vessels of the neck or far into the axilla. It is heard as well with the child erect as recumbent and is accompanied with a thrill. (It should be noted that this description does not cover all interventricular septal defects.)

C. Coarctation of the aorta

This diagnosis is readily established by comparing the blood pressure in the arms and in the legs; this procedure should be carried out whenever congenital heart disease is suspected. In all other patients, including cyanotic children, further studies are needed for accurate differential diagnosis.[5]

D. Possible congenital heart disease

These are generally systolic murmurs which are louder and harsher than the usual physiologic murmurs yet they are not characteristic of a definite congenital malformation.

III. Rheumatic fever or chorea

Rheumatic fever was suspected if a child was sick without apparent reason or had a recent history of migratory pains in the joints, nosebleeds, fever, tachycardia, abdominal pain or pallor for which no immediate explanation was at hand. Further

5. Taussig, H. B.: Congenital Malformations of the Heart, New York, Commonwealth Fund, 1947.

studies should be made and each case reported individually with the criteria of diagnosis. Choreiform movements are best observed when a child is making an effort to lie perfectly still for a minute or longer.

The conditions of those children in which, despite further study, an immediate decision could not be made were classified as possible rheumatic fever or chorea.

TABLE 1.—*Prevalence of Heart Disease and Rheumatic Fever Among Children Living at an Altitude of 10,000 Feet or Above*

Population at school age, estimated	1,454
Number of children examined	1,017
Disease	**% Patients**
Rheumatic heart disease	1.0
Possible rheumatic heart disease	0.7
Congenital heart disease	0.3
Possible congenital heart disease	0.9
Heart disease, type undetermined	0.1
Rheumatic fever or chorea	0.2
Possible rheumatic fever or chorea	0.3
History of Disease	**% Patients**
Inflammatory rheumatism	1.4
Rheumatic fever	2.8
Chorea	1.6
Scarlet fever	8.7
Family History of Disease	**% Patients**
Rheumatic fever	5.4
Inflammatory rheumatism	10.5
Chorea	6.8
Number of persons per room in patients' homes	0.9*

* This is an index number, not a percentage.

TABLE 2.—*Details of Findings in Children with Definite Rheumatic Heart Disease*

Case No.	Age, Yr.	Sex	Cardiac Findings*	History of Rheumatic Fever: Personal	History of Rheumatic Fever: Family	Length of Residence in County	Previous Diagnosis of Heart Disease
1	8	M	A. I.	No	No	44 mo.	No
2	8	M	M. I.	Yes	Yes	48 mo.	Yes
3	9	F	M. I.	Yes	No	Life	Yes
4	10	M	M. I.; M. S.	Yes	Yes	Life	Yes
5	12	F	M. I.	No	Yes	Life	Yes
6	12	M	M. I.	Yes	No	6 yr.	Yes
7	12	M	M. I.; M. S.; A. I.	No	No	Life	No
8	13	M	M. I.	No	Yes	Life	Yes
9	13	M	A. I.	No	No	1 mo.	No
10	15	M	M. I.; A. I.	No	No	Life	No

* *M. I.* indicates mitral insufficiency, *M. S.* mitral stenosis and *A. I.* aortic insufficiency.

RESULTS

Ten children had rheumatic heart disease (1 per cent), and 7 had possible rheumatic heart disease (0.7 per cent). There were 3 children who had congenital heart disease, 2 with a patent ductus arteriosus and 1 with an interventricular septal defect (0.3 per cent); 9 had possible congenital heart disease (0.9 per cent).

The number with possible congenital heart disease is high. Loud systolic murmurs over the pulmonary area were frequently heard, oftener than our experience at an altitude of 5,000 feet (1,524 meters) would have led us to expect. As the survey progressed, we gradually realized that these murmurs were physiologic.

One child had an unusual diastolic murmur along the left sternal border. His condition was called heart disease "type undetermined" because the murmur was not at all characteristic of pulmonary or aortic insufficiency and yet seemed organic.

The conditions of children with extremely elevated sedimentation rates (these were done on approximately 30 children) were classified as possible active rheumatic fever. One of these was examined later and was observed to have not active rheumatic fever but early otitis media. One child had chorea, and one child (case 7) with rheumatic heart disease had possible chorea. One additional child was seen in her home and observed to have active rheumatic carditis; she died two months later.

These results and information obtained from questionnaires filled out by the parents are summarized in table 1. Details of the findings in those children with definite rheumatic heart disease are given in table 2.

COMMENT

Rheumatic heart disease is not unusually prevalent or severe in children living at an altitude of 10,000 feet or above. These studies confirm previous work which indicated that the prevalence of rheumatic heart disease among children in Colorado is not unusual, although the death rate is high.[3] In a carefully selected group of seventh and eighth grade rural school children in Connecticut, Quinn reported a prevalence of 1.6 per cent,[6] which, on consideration of the age group examined, does not differ from a prevalence of 1 per cent among these children in Colorado living at an altitude of 10,000 feet.

There were 13 children attending school with heart disease. Seven were unaware of its existence. An additional 39 children with normal hearts had been told that they had heart disease or "leakage of the heart." Rapid examination of entire school populations by those qualified is the best method of finding cases of early rheumatic heart disease and also serves to remove the label of "cardiac" from the normal child. If all children with heart disease were identified and given the benefit of all possible therapeutic and prophylactic procedures, a substantial number of lives would be prolonged.

6. Quinn, R. W.: Rheumatic Heart Disease and Crowding, Am. J. Pub. Health **38**:1071 (Aug.) 1948.

SUMMARY

1. The prevalence of rheumatic heart disease among children in Colorado living at an altitude of 10,000 feet or above was determined, with the following results:

Altitude		Population at School Age	Total Number Examined	Per Cent with Rheumatic Heart Disease
Feet	Meters			
10,000	3,048	1,454	1,017	1.0

2. Rheumatic heart disease is not unusually prevalent or severe at this altitude.

3. This study supports the conclusion that the prevalence of rheumatic heart disease among children in Colorado is not unusual compared with that of other areas, although the death rate is high.

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ACUTE CONJUNCTIVITIS CAUSED BY HEMOPHILUS

DORLAND J. DAVIS, M.D.
AND
MARGARET PITTMAN, Ph.D.
BETHESDA, MD.

A SEVERE form of acute conjunctivitis occurring endemically and epidemically has been reported in Georgia, in California and also in other parts of southern United States.[1] The disease, which has been known as "pink eye," "sore eyes" or "gnat sore eyes," has a high incidence, especially among children, and is an important public health problem in affected areas. It was our privilege to investigate the problem in the Lower Rio Grande Valley of Texas at the invitation of the Hidalgo-Starr Counties Medical Society, extended through the National Society for the Prevention of Blindness. During the field investigations carried out in October 1947 and in May 1948, we used the clinical facilities of practicing physicians, the nursing service of the Hidalgo County Health Unit and the laboratory of the United States Public Health Service Dysentery Control Project. Clinical and epidemiologic data on several hundred patients in this region, and bacteriologic and therapeutic observations on a smaller number, form the basis of this report. A few patients in the vicinity of Washington, D. C., were also studied.

CLINICAL COURSE

As we observed it, the disease begins with watering and irritation of one eye, usually followed in a few hours by vascular injection of the conjunctiva and pain. The discharge soon becomes purulent, and the lids are often tightly adherent with dried exudate when the patient awakes in the morning. On the second or third day, the lids may become edematous and in severe attacks they are so swollen that the patient has difficulty in opening them. In many patients the other eye becomes involved a day or two after the original eye is affected.

From the Microbiological Institute, National Institutes of Health.

Read before the Section on Pediatrics at the Ninety-Eighth Annual Session of the American Medical Association, Atlantic City, N. J., June 8, 1949.

1. Bengtson, I.: Seasonal Acute Conjunctivitis Occurring in the Southern States, Pub. Health Rep. **48**:917, 1933. Schneider, A.: An Introductory Report on Pseudo-Trachoma Endemic in the Salton Sea Region of California, M. Sentinel **33**:154, 1927. Rice, C. E.: Personal communication to the authors.

Usually, the conjunctivas are severely inflamed, and there may be ecchymoses of the bulbar conjunctivas. Photophobia, pain and tenderness are prominent features at this stage, and phlyctenules may appear on the cornea. However, most attacks do not progress to this degree of severity and all gradations of the disease may be seen, including mild conditions with only slight vascular injection and irritation lasting a few days. Rarely is there enlargement or tenderness of the preauricular lymph nodes. Many patients, particularly children, show a slight elevation of temperature of 1 to 2 degrees (F.). There appears to be no sequelae, and the signs and symptoms gradually regress over a period of several weeks in untreated patients.

EPIDEMIOLOGIC ASPECTS

Epidemiologic observations indicate that the disease is largely one of infants and young children. In a series of 473 cases (table 1), reported to visiting nurses in the households of certain families under

TABLE 1.—*Age Distribution of Four Hundred and Seventy-Three Patients with Clinical Conjunctivitis in Hidalgo County, Texas*

Age, Yr.	No. Patients	Per Cent
0 to 4	270	57.2
5 to 9	118	25.0
10 to 14	26	5.4
15 to 19	8	1.7
20 and older	51	10.7
Total	473	100.0

observation in connection with the United States Public Health Service Dysentery Control Project, 57 per cent of the patients were under 5 years of age and 25 per cent were 5 to 9 years old. There was no difference in sex distribution.

The aggregation of the disease within the family is shown by the calculation of age-specific familial attack rates determined from the detailed histories of a group of 27 families which were personally investigated. These represent attacks occurring within two months of the onset of the index case (the first case observed in the family). It is apparent from table 2 that nearly half the children under 5 years of age exposed to a person in the family with the acute disease acquired the disease, and a total of one fourth of those exposed at all ages were attacked.

One attack appeared to confer little, if any, protection against later attacks, since approximately 16 per cent of 118 patients for whom data were available were reported as having had a previous attack within six months. Some children had recurrent attacks every month for a period of several months.

The disease was reported by physicians to be commonest during the warm months of the year, particularly the early fall, and was seen in both urban and rural areas. Immigrant Mexican agricultural workers were heavily attacked, and the disease assumed great importance as a cause of absence from school and work.

The exact means of transmission of the disease is not known, but many physicians and others are of the opinion that the eye gnat, Hippelates pusio, may serve as a vector of the causative agent. These gnats are particularly abundant during the warm months and are attracted by the moist mucous membranes of man or animals. They are frequently seen clustered about the eyes of infants, particularly if exudate is present. Gnats could act as a mechanical means of transfer, but their importance, if established, would have to be evaluated in relation to transmission of infectious material by fingers, clothing, towels or other fomes.

TABLE 2.—*Age-Specific Secondary Attack Rate of Conjunctivitis in Twenty-Seven Families*

Age, Yr.	No. Persons Exposed	No. Persons Attacked	Per Cent
0 to 4	33	17	48.5
5 to 9	28	9	32.1
10 to 19	27	8	29.6
20 and older	60	3	5.0
Total	150	37	24.6

ETIOLOGIC FACTORS

During the course of our investigations in the Rio Grande Valley, a total of 123 cases of acute conjunctivitis occurring in persons of all age groups was studied in detail to determine the cause of the disease. Bacterial cultures were made on all patients by swabbing the conjunctiva with a moistened cotton swab, incubating the swab at 37 C. (98.6 F.) in 0.15 per cent nutrient agar containing 2.0 per cent Fildes' peptic digest of sheep blood [2] for two to three hours. The swab was then streaked on a beef heart infusion agar plate containing Fildes' peptic digest of blood and, in many instances, on a blood agar plate. Scrapings of the conjunctiva and exudate were smeared and stained with the Machiavello and the Gram stains in most cases. For the first 45 patients studied, scrapings of the conjunctiva and exudate were suspended in milk, quickly frozen and shipped back to our laboratory in Bethesda, Md. This material was inoculated by various routes and

2. Fildes, P.: A New Medium for the Growth of B. Influenzae, Brit. J. Exper. Path. **1**:129, 1920.

under a variety of conditions into large series of laboratory animals and embryonated chicken eggs, but no evidence of any pathogenic agent was secured.

From the original bacterial cultures small gram-negative bacilli belonging to the genus Hemophilus and requiring both X and V growth factors were isolated from approximately one-half the patients. After considerable study, we were able to separate these strains into two groups. One group consisted of strains of Hemophilus influenzae (Pfeiffer's bacillus). The majority of these were non-type-specific, but a few strains were encapsulated and type specific. The other group consisted of strains which resembled H. influenzae in certain respects but differed from it in others and corresponded to the original descriptions of the Koch-Weeks bacillus.[3]

The so-called Koch-Weeks bacillus was first seen in Egypt in conjunctival smears by Koch in 1883 and first cultured by Weeks in New York city in 1886. It has long been incriminated as a cause of acute contagious conjunctivitis in certain parts of Europe, South America and Egypt.

H. influenzae, frequently associated with respiratory and meningeal infection, has also been reported as causing conjunctivitis. Probably in many instances this organism has been incorrectly designated the Koch-Weeks bacillus because of its isolation from the conjunctiva. This practice has caused confusion in identification of the cultures, for which there were no generally recognized differential criteria. Many textbooks and taxonomies [4] have considered them as the same species. Recently, we reported [5] studies carried out with the strains isolated in Texas in which means of differentiating the two species were established.

The Koch-Weeks bacillus tends to be more elongated morphologically, multiplies more slowly and dies out more readily in culture than H. influenzae. It does not produce indole or ferment xylose, while the majority of H. influenzae strains do. It forms a relatively homogenous serologic group according to agglutination with specific immune rabbit serum, while non-type-specific H. influenzae does not. The Koch-

3. Koch, R.: Bericht über die Thätigkeit der deutschen Cholerakommission in Aegyptein, Wien. med. Wchnschr. **33**:1548, 1883. Weeks, J. E.: The Bacillus of Acute Conjunctival Catarrh or "Pink Eye," Arch. Ophth. **15**:441, 1886; The Pathogenic Microbe of "Acute Catarrhal Conjunctivitis," M. Rec. **31**:571, 1887.

4. Lehmann, K. B., and Neumann, R. O.: Bakteriologie, inbesondere bakteriologisch Diagnostik, ed. 7, München, J. F. Lehmann, 1927, vol. 2, p. 313. Bergey, D. H.: Bergey's Manual of Determinative Bacteriology, edited by R. S. Breed and others, ed. 6, Baltimore, Williams & Wilkins Company, 1948, p. 585.

5. Pittman, M., and Davis, D. J.: Identification of the Koch-Weeks Bacillus, read at the Forty-Ninth General Meeting of the Society of American Bacteriologists, Cincinnati, May 18, 1949, to be published, J. Bact., 1950, vol. 59.

Weeks bacillus also possesses an agglutinin for human red blood cells not demonstrated by H. influenzae.[6]

Now that these methods of differentiation are available, it may be possible to determine differences in pathogenesis, clinical course, distribution in the United States and, possibly, mode of transmission in infections caused by the two organisms.

Of the 123 patients for whom bacteriologic cultures were made in Texas, pathogenic organisms were recovered from 68 cultures (table 3). The Koch-Weeks bacillus was isolated and identified from 29, and probably also from 16 more which were lost before final identification, though the organisms were shown to be of the genus Hemophilus. Cultures from 15 were of H. influenzae (Pfeiffer's bacillus), including 3 of type-specific strains, and there was 1 of Hemophilus parainfluenzae. Other pathogens occurring only sporadically were Moraxella sp. and unidentified streptococci and pneumococci.

TABLE 3.—*Pathogens Recovered from One Hundred and Twenty-Three Persons with Conjunctivitis in Hidalgo County, Texas*

	No. Patients	Total
Hemophilus group		
Koch-Weeks bacillus	29	
Probable Koch-Weeks bacillus lost before final identification	16	
H. influenzae (Pfeiffer's bacillus), including 3 type-specific strains	15	
H. parainfluenzae	1	
		61
Other		
Moraxella sp.	1	
Probable Moraxella	3	
Streptococci (not identified)	2	
Pneumococci (not identified)	1	
		7
Total		68
No. with no recognized pathogens		55

From 55 patients no pathogens were recovered. However, our technics may not have been adequate, since cultures were made only once from each patient; many were infants for whom it was difficult to make cultures, and some had received medication. Furthermore, some of the plates were overgrown with spreading colonies.

Although the Koch-Weeks bacillus was recovered from a large proportion of the patients (45 of the 123 patients) and many times in almost pure culture, additional evidence was secured by 8 experimental human infections[7] to demonstrate its role as the cause of the disease.

6. Davis, D. J.; Pittman, M., and Griffitts, J. J.: Hemagglutination by the Koch-Weeks Bacillus, read before the Forty-Ninth General Meeting of the Society of American Bacteriologists, Cincinnati, May 18, 1949, to be published, J. Bact., 1950, vol. 59.

7. Davis, D. J., and Pittman, M.: The Effectiveness of Streptomycin in Treatment of Experimental Conjunctivitis Caused by Hemophilus sp., Am. J. Ophth. **32**:111 (June, pt. 2) 1949.

This study revealed that a culture of the Hemophilus organism subsequently shown to be the Koch-Weeks bacillus produced typical disease in 6 of 8 adult human subjects. It also indicated that streptomycin was effective in treatment of the experimental disease.

After the clarification of the differentiating characteristics of the Koch-Weeks bacillus and H. influenzae, 2 adult subjects were inoculated in the conjunctival sac with a broth culture of a non-type-specific H. influenzae strain (no. 697), recently isolated from a child with acute conjunctivitis, to determine its pathogenicity. The clinical reaction was mild yet definite, with moderate exudate and slight injection the major features. As shown in the chart, H. influenzae, the inoculated organism, was recovered from the affected eyes until streptomycin therapy was instituted. In 1 subject there was a recurrence on the twelfth day.

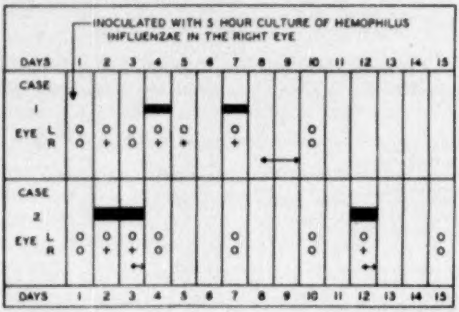
INOCULATED WITH 5 HOUR CULTURE OF HEMOPHILUS INFLUENZAE IN THE RIGHT EYE
DAYS 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
CASE 1
EYE L R
CASE 2
EYE L R
DAYS 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

Chart showing course of experimental conjunctival infection with H. influenzae in 2 human subjects. Plus signs indicate days on which H. influenzae was isolated, zeros days on which the organism was not isolated, solid bars days of clinical symptoms and arrows duration of streptomycin therapy.

Although the 2 experimental H. influenzae conjunctival infections were less severe than the experimental infections with the Koch-Weeks bacillus, the number of affected persons is too small to give a valid comparison of clinical severity. In the naturally occurring infections among children and infants, the disease caused by either of the two species of Hemophilus presented similar signs and symptoms in our small series of patients and could not be clinically distinguished. A larger series will have to be observed before data concerning differences in clinical course or epidemiologic aspects are secured.

THERAPY

In the experimental human infections treatment with streptomycin appeared to be beneficial. Therefore, an investigation was undertaken in Hidalgo County to observe therapeutic results in naturally occurring

TABLE 4.—*Data on Thirty Patients with Conjunctivitis Caused by Koch-Weeks Bacillus or H. influenzae Treated with Streptomycin or Zinc Sulfate and Followed by Bacteriologic Cultures*

Case No.	Sex	Age, Yr.	Duration Before Treatment, Days	Organism Present Before Treatment	Treatment	Cultures After Start of Treatment *			Clinical Results in 24 Hr.
						4 Hr.	24 Hr.	48 or More Hr.	
1	M	5	30	Koch-Weeks bacillus†	Streptomycin solution, 0.1%	—	—	0	Improved
2	M	12	8	Koch-Weeks bacillus	Streptomycin solution, 0.1%	0	—	—	Improved
3	M	8	2	Koch-Weeks bacillus	Streptomycin solution, 0.1%	—	—	0	Improved
4	M	3	2	Koch-Weeks bacillus	Streptomycin solution, 0.1%	—	0	0	No record
5	M	5	4	Koch-Weeks bacillus	Streptomycin solution, 0.1%	—	0	0	No record
6	F	10/12	4	Koch-Weeks bacillus	Streptomycin solution, 0.1%	0	—	0	Improved
7	F	3	40	Koch-Weeks bacillus	Streptomycin solution, 0.1%	0	+	—	Improved
8	F	5	5	Koch-Weeks bacillus	Streptomycin solution, 0.1%	0	—	—	Improved
9	F	8	2	Koch-Weeks bacillus	Streptomycin ointment, 0.5%	0	0	—	Improved
10	M	7	3	Koch-Weeks bacillus	Streptomycin ointment, 0.5%	0	0	—	Improved
11	M	5	4	Koch-Weeks bacillus	Streptomycin ointment, 0.5%	0	0	—	Improved
12	M	4	4	Koch-Weeks bacillus	Streptomycin ointment, 0.5%	0	0	—	Improved
13	M	6/12	3	Koch-Weeks bacillus	Streptomycin ointment, 0.5%	0	0	—	Improved
14	F	8/12	2	Koch-Weeks bacillus	Streptomycin ointment, 0.5%	0	0	—	Improved
15	F	12	5	Koch-Weeks bacillus	Streptomycin ointment, 0.5%	0	0	—	Improved
16	F	14/12	7	Koch-Weeks bacillus†	Zinc sulfate solution, 0.25%	+	—	0	Improved
17	F	2	14	Koch-Weeks bacillus†	Zinc sulfate solution, 0.25%	—	—	0	Improved
18	F	3	20	Koch-Weeks bacillus†	Zinc sulfate solution, 0.25%	0	—	—	Improved
19	M	12	3	Koch-Weeks bacillus	Zinc sulfate solution, 0.25%	+	—	—	Improved
20	M	9	6	Koch-Weeks bacillus	Zinc sulfate solution, 0.25%	0	—	—	Improved
21	F	7	20	H. influenzae	Streptomycin solution, 0.1%	—	—	0	Improved
22	F	4	3	H. influenzae	Streptomycin solution, 0.1%	+	—	0	Improved
23	M	11	10	H. influenzae	Streptomycin solution, 0.1%	—	—	—	Improved
24	F	9	90	H. influenzae	Streptomycin solution, 0.1%	0	—	0	Improved
25	F	4/12	2	H. influenzae	Streptomycin solution, 0.1%	+	—	—	Improved
26	M	14/12	3	H. influenzae	Streptomycin solution, 0.1%	0	+	—	Improved
27	M	9/12	4	H. influenzae	Streptomycin ointment, 0.5%	0	0	—	Improved
28	F	3/12	90	H. influenzae	Streptomycin and zinc sulfate	+	—	+	Not improved
29	F	11/12	30	H. influenzae	Zinc sulfate solution, 0.25%	—	—	—	Improved
30	M	11	5	H. influenzae	Zinc sulfate solution, 0.25%	—	—	—	Improved

* Plus sign indicates Hemophilus organisms were recovered, the minus sign that they were not recovered and the zero that no culture was made.
† Strain lost before final serologic confirmation.

infections under clinical conditions. For this part of the study 73 patients coming to the McAllen Child Clinic, McAllen, Texas, with the complaint of "sore eyes" were examined, brief histories recorded and conjunctival cultures taken. Some patients were treated with streptomycin, and others were treated with zinc sulfate U. S. P. as basis of comparison with the streptomycin therapy.

Streptomycin was applied as a 0.1 per cent solution in 0.85 per cent sodium chloride solution either with an eye cup or, in infants, with an eye dropper. Some patients were treated with 0.5 per cent streptomycin ophthalmic ointment.[8] Zinc sulfate was used as a 0.25 per cent solution in an eye cup or by dropper. After the initial treatment, all patients possible were kept at the clinic and treated again two hours later; then four hours later cultures were made and the patients were treated again. The patient, or the parents, was provided with the medicament and instructed to continue treatment at home every two

TABLE 5.—*Recovery of Hemophilus After Treatment in Thirty Persons with Conjunctivitis*

	No. of Patients with Positive Cultures Before Treatment			Cultural Results in Patients After Treatment					
				4 Hr.		24 Hr.		48 Hr. or More	
Treatment	Koch-Weeks Bacillus	H. Influenzae	Total	No. with Cultures	No. Positive	No. with Cultures	No. Positive	No. with Cultures	No. Positive
Streptomycin	15	7	22	8	2	12	2	14	0
Zinc sulfate	5	3	8	6	3	8	0	6	1

hours and to return on successive days for observation and reculture. Therapy was continued for three days, then stopped completely.

Sixty of these 73 persons were observed subsequently, and in all but 3 there was definite clinical improvement. For 30 patients either the Koch-Weeks bacillus or H. influenzae was isolated from the culture material taken preceding treatment, and in each patient the effect of treatment was followed by cultures. The data concerning these 30 patients are presented in table 4 and summarized in table 5. The Koch-Weeks bacillus was originally isolated from 20 patients and H. influenzae from 10.

Twenty-two patients were treated with streptomycin and 8 were treated with zinc sulfate. They ranged in age from 3 months to 12 years, and one half of them had had the infection four days or less. Among the remainder, 5 had had the disease for a month or longer. The table shows that cultures taken four hours after treatment were positive in only 2 of 8 children treated with streptomycin for whom cultures were made and in 3 of 6 treated with zinc sulfate for whom

8. This ointment was furnished by Eli Lilly & Company, Indianapolis.

cultures were made. At twenty-four hours 2 of 12 treated with streptomycin and none of the 8 treated with zinc sulfate had positive cultures when they were examined. After forty-eight hours or more, only 1 child, a cachectic 3 month old infant with a severe infection of the upper respiratory tract, still harbored H. influenzae in the conjunctiva.

While the treatment schedules appeared to be beneficial, we did not determine whether other methods or regimens of application of streptomycin or zinc sulfate would be as effective or less so. However, our observations impressed us with the importance of proper administration of either drug so that a sufficient concentration reaches the infected conjunctiva for an adequate length of time. In persons with conjunctivitis with concurrent infection of the upper respiratory tract there is the possibility of reinfection after treatment. This was observed in one patient (case 28) seen in Hidalgo County and also noted in several patients seen near Washington, D. C. Clinical improvement was manifested by diminished conjunctival exudate and secretion and reduced pain, then later by lessened vascular injection. In some patients the improvement appeared as early as four hours after treatment was started.

In the vicinity of Washington, D. C., a number of patients with acute conjunctivitis have been observed during the late winter months. From 9 of these persons, including 3 adults and 6 children under 5 years old, non-type-specific H. influenzae was recovered in almost pure culture. In nearly every one of these patients the conjunctivitis was preceded by an infection of the upper respiratory tract which persisted during the ocular infection. The response to streptomycin therapy was prompt, though several of the infections tended to recur about seven days later, but then promptly cleared with further streptomycin treatment.

SUMMARY

A severe form of acute conjunctivitis, characterized by vascular injection, purulent exudate, pain and, often, palpebral edema, was observed in the lower Rio Grande Valley of Texas. Infants and children were attacked more commonly than adults, and there was a high familial incidence. The principal cause of the infection was the Koch-Weeks bacillus, although a number of attacks were caused by Hemophilus influenzae. These two species can now be differentiated. Conjunctivitis caused by H. influenzae only was observed in the vicinity of Washington, D. C. The disease caused by both organisms responded well to streptomycin therapy and also to zinc sulfate therapy, as judged by subsequent clinical improvement and bacterial cultures negative for the organisms.

Microbiological Institute, National Institutes of Health (14).

ABSTRACT OF DISCUSSION

Dr. James C. Overall, Nashville, Tenn.: Dr. Davis and Dr. Pittman have brought us an important research report on a common clinical condition. "Pink eye" is a recurrent problem, especially in the spring, to both the pediatrician and the ophthalmologist. The pediatrician is inclined to treat the usual simple acute conjunctivitis as a minor problem. He may tell the mother to bathe or irrigate the child's eye often enough to keep it clean, with either boric acid or saline solution. In addition, zinc sulfate solution or penicillin ointment are frequently used. The mother may be told to return with the child in a day or two if the eye is not well.

In children conjunctivitis is often associated with certain acute generalized infections, such as measles, the common cold and influenza. This type is almost impossible to distinguish clinically from ordinary "pink eye." Here, also, the mother is given instructions to keep the eye clean and, in addition, to apply some lubricating ointment such as 1 per cent yellow mercuric oxide ointment or simple petrolatum. If, clinically, the infection is considered to be of the serious type, smears or scrapings and cultures are made.

The usual criteria for recognizing the severe infections are excessive swelling of the lids, especially the upper (the Koch-Weeks bacillus frequently spares the upper lid), pronounced redness and abundant, thick, purulent discharge. The treatment in these severe infections depends, of necessity, on the organism found. However, occasionally epidemics of real "pink eye," such as the one described here, do occur, and then stricter measures in diagnostics, isolation and treatment are employed. Fortunately, we have not had a real epidemic in Nashville recently, but they occur all over the world; in fact, I believe the original one reported by Weeks took place in New York. They occur chiefly in the spring, affect both eyes and rarely cause corneal ulcers; also, because of the lack of affinity for the lid, they seldom become chronic.

It is interesting to note that about 60 per cent of Dr. Davis's patients were in the preschool group. This might indicate that the infection is not quite so contagious as is thought, but it is more likely that immunity has developed in the older children from previous infection. It also seems significant that the patients responded about equally well to zinc sulfate solution and streptomycin. This certainly ought to make zinc sulfate solution the preferred medicament. In this way, we could avoid possible sensitization of the patient to streptomycin, as well as possible resistant strains of the organism.

This report of Dr. Davis and Dr. Pittman should make all of us more careful in our observation and treatment and stricter in our diagnosis of simple acute conjunctivitis.

Dr. Samiye Argut, Ankara, Turkey: I should like to make a geographic division of Turkey with respect to conjunctivitis. In the eastern and southeastern parts of the country conjunctivitis occurs as papillary conjunctivitis or trachoma. In the middle east mostly vernal conjunctivitis has been seen. In the rest of the country conjunctivitis occurs endemically and epidemically in every form, except that there are few cases of the first two aforementioned types. This disease appears to be commonest during the warm months of the year.

As I am an obstetrician, I am not able to say much about the work that has been done or that is now being done in bacteriologic and therapeutic study of the disease. I can give you only general statistics, which come from the outpatient service of Ankara Numune Hospital.

During the year 1948, there were 3,762 cases of conjunctivitis, of which 894 were pneumococcic conjunctivitis, 730 were Koch-Weeks, 675 were angular conjunctivitis caused by the Hemophilus (diplobacillus) of Morax-Axenfeld, 640 were

allergic or phlyctenular conjunctivitis and 823 were other types. I have not seen any gonorrheal infection or any conjunctivitis of the newborn. Silver nitrate prophylaxis is obligatory.

As far as recurrence is concerned, there is a big program under way to reduce the incidence of trachoma in the eastern part of the country. Many physicians, visiting nurses and dispensaries are necessary for the diagnosis, treatment and prevention of the disease. Data on the treatment and response of the individual cases were not available. I shall write my colleagues in Turkey about the valuable work that has been done by Dr. Davis and Dr. Pittman on this subject in the United States, and I hope that next year a representative from Turkey will be able to give you more detailed information on methods used there.

Dr. Thomas D. Allen, Chicago: My statements have to do with the clinical and practical aspects of this pandemic as I saw it and as I discussed it with the physicians who have had to fight the disease for years.

In January 1947, at the request of Dr. Edward W. Griffey, of Houston, and Dr. Edmond D. Wells, of Weslaco, Texas, I visited the Rio Grande Valley, where in a period of two days I saw about 30 cases of a pandemic of acute follicular conjunctivitis, known for many years in the valley as "Mexican sore eyes." I was amazed at the prevalence and severity of the disorder.

Dr. Wells and the other physicians in the valley had tried, without avail, apparently, the usual remedies—silver nitrate, boric acid, zinc sulfate, penicillin and several of the new sulfonamides. The disease seemed to be self limited, with a duration of about three weeks, but once in a family it was passed from one member to another and back to the first often before he had recovered from his first attack. This was especially true in children. There was apparently little, if any, immunity. Seldom was the cornea affected deeper than the epithelium; exceptionally, a corneal ulcer developed.

The clinical picture was typical: a conjunctival flush and tearing the first day, with swelling or edema, redness of the eyelids and some mucopus in the next twenty-four to forty-eight hours. This usually increased until the eyelids could scarcely be opened. There were, in such cases, considerable photophobia and usually some staining of the cornea, but not much tenderness of the eyeball itself. Often a palpable and tender preauricular gland was present. After a few days, the swelling began to subside, but the conjunctivas remained hyperemic and the follicles, which could be seen on the second day, usually remained, especially in the fornices. This led some of the physicians to consider a diagnosis of trachoma. However, there was no scarring in the conjunctivas or corneas such as is found in trachoma.

Dr. Wells had been treating the eyes with boric acid and ordinary yellow petrolatum. He was of the opinion that the patient would carefully wipe away the petrolatum as soon as he reached home, and this in itself would mean a certain amount of cleanliness. Many of the patients were poor and dirty, living in the most primitive manner, but clean persons were also affected, although among them it was usually the children who were infected. For example, 2 children of one of the physicians in a nearby town were infected. Seldom was the disease seen in only one eye.

Apparently, the disease has been pandemic in the valley for over fifty years, as a physician who had been there nearly fifty years said his early patients had known of it for a long time. I was told that almost every year at about the time school opened it became epidemic. The gnat season coincided with the opening of the school year, and some thought the gnats conveyed the disease.

It was impossible for me in the few days I spent in the valley to find the cause or the remedy. I, therefore, asked the National Society for the Prevention of

Blindness to bring pressure to bear on our public health officials to send an epidemiologic team to study the situation. They came; they saw; they conquered. They came first in October 1947 and again in May 1948. They have isolated two organisms, grown them in culture and infected volunteers who showed the typical symptoms and from whose eyes the organism could be recovered. Not only did they find the etiologic organism but they observed that one of the newer therapeutic agents, streptomycin, was quite effective, curing the disease in a few days. This experience should teach us to use the resources which as a nation we have developed.

May I take this opportunity to thank the essayists for their careful scientific study of this problem, which should help us eliminate this serious disorder and make the valley even more attractive? In conclusion, may I suggest that the essayists and others interested in this problem see the exhibit of Dr. F. H. Theodore, which is in the Section on Ophthalmology of the Scientific Exhibit?

Dr. Alson E. Braley, New York: From the past work of Dr. Davis and Dr. Pittman on the Hemophilus group, we know that they are authorities on this group of organisms. They have contributed much to what we already know about this difficult group of micro-organisms, and they have brought some degree of order to its chaos. Although the present observations show a differentiation between the Koch-Weeks bacillus and Hemophilus influenzae, one would gather from almost all the bacteriology books that they are identical organisms. For many years, I have been certain that they were two different organisms, but most of this impression has not been based on scientific grounds. They are not the same organisms because clinically they do not produce the same type of disease. The Koch-Weeks bacillus produces a purulent conjunctivitis, while H. influenzae produces a milder type of conjunctivitis, and, when experimentally inoculated into the conjunctiva, it produces a relatively mild conjunctivitis.

I am not sure of some of the past work and differentiation culturally, but the authors' serologic tests with red cells seem to be adequate. The age of the patients and the incidence in the epidemic as it occurred in Texas seemed to be of the preschool group, which would indicate either a susceptibility to infection or the transmission of this infection to the younger children by some agent. I suspect that it probably was the former.

The fact that the authors grew the organism from only about 50 per cent of the patients does not disturb me too much, because I know that the organism is not easily grown and many times requires special methods. I should, however, like to know whether epithelial scrapings were taken of the conjunctivas. It has been my experience in the case of Koch-Weeks infection that one finds a large number of organisms in the scrapings, whereas in H. influenzae infection few organisms are present.

Although I see a fair number of patients with influenzal infections, I have used local application of aureomycin with what I think is even better success than that obtained in the past by treatment with streptomycin and zinc sulfate.

Dr. Dorland J. Davis, Bethesda, Md.: I am glad that Dr. Argut emphasized the extent of conjunctivitis throughout the world, particularly in her home country of Turkey. In answer to Dr. Braley's question concerning epithelial scrapings, they were taken from many of the cases and the Koch-Weeks bacillus was found in the smears. I agree with him that the Koch-Weeks bacillus was much easier to find than the Hemophilus influenzae was. However, we did not depend on finding the organism in the smear for our diagnosis but relied on the isolation of the culture which we felt was much more trustworthy. I am glad that Dr. Braley mentioned his work with aureomycin in the treatment of Hemophilus conjunctivitides, because it adds another medicament for this group of diseases.

EPILEPSY IN TWINS

An Analysis of Five Twin Pairs, with Electroencephalographic Studies

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BIRMINGHAM, ALA.
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NEILL K. WEAVER, M.D.
NEW ORLEANS

IT IS now generally recognized that convulsive disorders, or epilepsy, are associated with a disturbance in the electrical activity of the brain, a cerebral dysrhythmia. The convulsive disorder and the cerebral dysrhythmia may result from genetic and/or acquired influences. The inheritance of monozygotic (single ovum) twins is similar, while the inheritance of dizygotic (double ovum) twins is the same as that of ordinary siblings. Studies of twin pairs are, therefore, of great importance in evaluating the influence of "heredity" and "environment" in the production of convulsive disorders. As the brain wave pattern has been shown to be a hereditary trait,[1] electroencephalographic studies are a useful adjunct in the study of twins.[2]

Information gained from the study of twins is necessarily restricted by the small numbers available for investigation, and most reports in the past have dealt with only a few twin pairs.[3] Lennox was able to collect 66 twin pairs affected by seizures over a period of about twelve years.[4] The present report is a detailed analysis of 5 twin pairs which

From the Division of Neurology, Department of Medicine, Medical College of Alabama, Birmingham, Ala., and the Department of Internal Medicine, Tulane University School of Medicine, New Orleans.

1. Lennox, W. G.; Gibbs, E. L., and Gibbs, F. A.: The Brain Wave Pattern: An Hereditary Trait, J. Hered. **36**:233-243 (Aug.) 1945.

2. Lennox, W. G.; Gibbs, E. L., and Gibbs, F. A.: Inheritance of Cerebral Dysrhythmia and Epilepsy, Arch. Neurol. & Psychiat. **44**:1155-1183 (Dec.) 1940. Fabing, H.: Tuberous Sclerosis with Epilepsy (Epiloia) in Identical Twins, Brain **57**:227-238 (Oct.) 1934. Lennox, W. G., and Gibbs, E. L.: The Intelligence and the Electroencephalograms of Normal and Epileptic Twins, Tr. Am. Neurol. A. **70**:182-184, 1944.

3. Hobbs, G. E.: Mental Disorder in One of a Pair of Identical Twins, Am. J. Psychiat. **98**:447-450 (Nov.) 1941. Freeman, W.: Symptomatic Epilepsy in One of Identical Twins: Study of Epileptic Character, J. Neurol. & Psychopath. **15**:210-218 (Jan.) 1935.

4. Lennox, W. G.: Sixty-Six Twin Pairs Affected by Seizures, A. Research Nerv. & Ment. Dis., Proc. **26**:11-34, 1947.

will also be included in the most recent report on this subject by Lennox.[5]

METHOD AND MATERIAL

The 10 persons who are the basis of this report were observed in the clinics for neurologic and convulsive disorders of the Medical College of Alabama or in the private practice of one of us (S. C. L.) during a period of three years. Three of the persons were studied during periods of hospitalization. In all patients special effort was made to inquire concerning a past history of brain injury, a family history of disorders of consciousness and the exact type of seizures present. When one co-twin was presumed to be normal, all means were utilized to detect even a suspicion of a convulsive disorder.

Zygosity (whether of single egg or double egg origin) was determined in all instances beyond reasonable doubt by the method of similarity[6] and by studies of blood groupings and/or fingerprints. Electroencephalograms were obtained in the usual fashion, using a four or eight channel ink-writing oscillograph. Representative sections from the electroencephalograms are shown in figures 1 to 5.

REPORT OF CASES

Twin Pair 1.—F. L. B. and L. B. were monozygotic twin boys, 4 years of age. F. L. B. had had seizures since the age of 16 months or before. They were of akinetic and tonic type, and massive myoclonic jerks also occurred. Status epilepticus had been noted on at least one occasion. The frequency of seizures became greater following an injury to the head at the age of 30 months, and the seizures occurred several times daily. After administration of trimethadione (tridione®) was begun, the seizures were almost completely suppressed. Neurologic examination at the age of 28 months showed left hemiparesis which gradually improved.

L. B., the co-twin, showed no evidence of a convulsive disorder or of organic brain deficit.

The mother died a few hours after delivery. The circumstances of birth are unknown. There was no family history of disorders of consciousness or of nervous or mental disease.

Electroencephalographic Findings.—The record (fig. 1*A*) of F. L. B. showed almost continuous 2 per second wave and spike dysrhythmia which was somewhat more pronounced on the right. The record (fig. 1*B*) of the normal co-twin, L. B., was classified as borderline, with questionably paroxysmal 4 per second patterns, but it showed much less abnormality than that of his twin.

All criteria indicated that these twins were monozygotic.

Pair Analysis.—These children were monozygotic twins, one normal, the other having a convulsive disorder which was probably the result of acquired disease

5. Lennox, W. G.: Paper read before International Neurological Congress, Paris, France, Sept. 5 to 10, 1949.

6. Newman, H. H.: Multiple Human Births: Twins, Triplets, Quadruplets and Quintuplets, American Association for the Advancement of Science, Series 1, New York, Doubleday, Doran & Company, Inc., 1940. Guttmacher, A. F.: Life in the Making, New York, Viking Press, Inc., 1933, pp. 240-287.

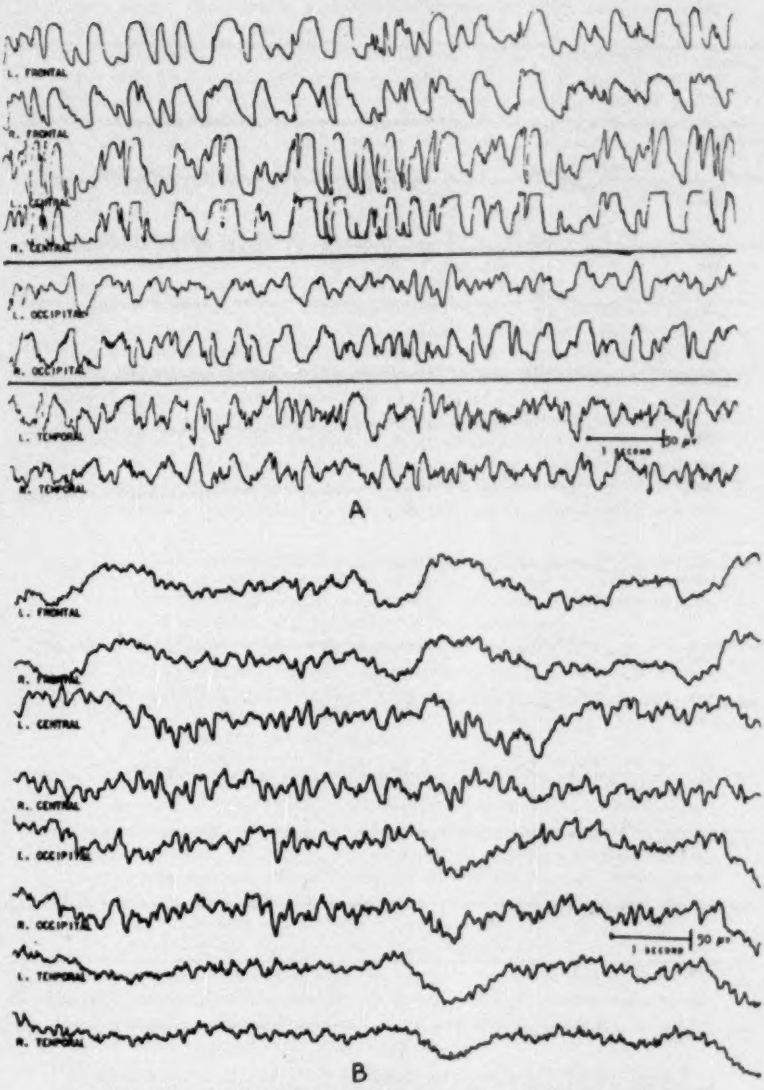

Fig. 1 (twin pair 1).—Electroencephalograms of monozygotic twin boys. *A*, made May 18, 1948, is of F. L. B., 3 years of age, who had grand mal, myoclonic, akinetic and status epilepticus seizures since 16 months of age which may be post traumatic. *B*, made April 4, 1949, is of L. B., his twin brother, 4 years of age, who had no seizures and no febrile convulsions and showed a borderline paroxysmal tracing.

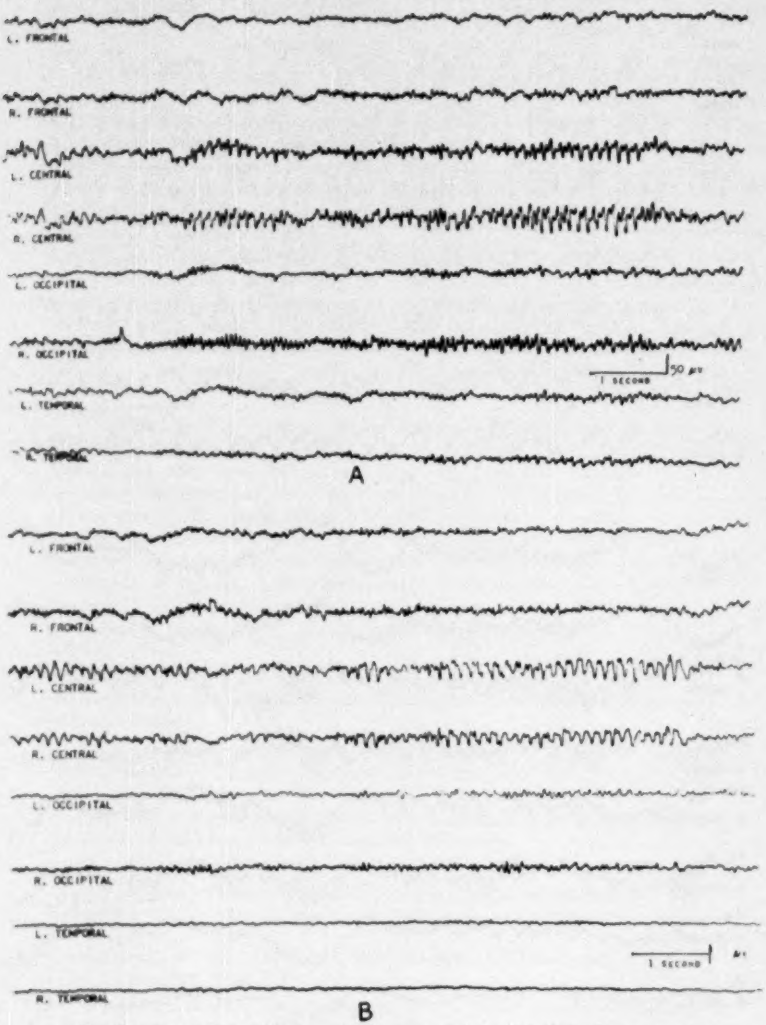

Fig. 2 (twin pair 2).—Electroencephalograms made April 9, 1949 of monozygotic female twins, 24 years of age. *A* is of J. G. B. who had infrequent grand mal seizures, and *B* is of R. C. W. who had no seizures of any kind at any time.

of the brain. There was no family history of seizures. Electroencephalographic studies bore out the clinical impression.

TWIN PAIR 2.—J. G. B. and R. C. W. were female monozygotic twins, 24 years of age.[7] J. G. B.'s first seizure occurred at the age of 21 years and was of generalized grand mal type. The seizures recurred about three times a month prior to institution of therapy and were completely suppressed by use of diphenylhydantoin sodium. There was no history suggestive of organic disease of the central nervous system. Results of neurologic examination were normal.

R. C. W. had had no disorders of consciousness whatsoever, and there was no evidence of any disease of the central nervous system.

On the paternal side the grandfather and an uncle had had grand mal seizures.

Electroencephalographic Findings.—The record (fig. 2*A*) of J. G. B., the affected twin, showed paroxysmal, medium to high voltage 7.5 to 8 per second activity in the central areas, with superimposed 16 to 18 per second activity. In the occipital regions 16 to 18 per second activity was seen and was much more prominent on the right. All fast frequencies were increased in amount and amplitude by hyperventilation. The record (fig. 2*B*) of R. C. W. was similar to that of her twin. All the features noted in the record of J. G. B. were present in her record but in lesser degree. A feature not present in her twin's record was the occasional occurrence of bursts of medium voltage 20 to 22 per second activity in the central regions. The records in this pair were strikingly similar, the dysrhythmia being more pronounced in the affected twin.

All criteria indicated that the twins were monozygotic. Blood typing was not done.

Pair Analysis.—These women were monozygotic twins, one clinically normal, the other with "cryptogenic" grand mal seizures. There was a family history of seizures. Electroencephalographic findings were strikingly similar, both showing a dysrhythmia which was most pronounced in the affected twin.

TWIN PAIR 3.—M. W. and I. W. were monozygotic twin girls, 9 years of age. M. W. had had frequent grand mal seizures since the age of 2 years. The seizures were well controlled by administration of diphenylhydantoin sodium. There was no history of any injury to or infection of the central nervous system, and neurologic examination gave normal results.

I. W., the co-twin, had had no disorders of consciousness at any time and was clinically normal. The mother had grand mal seizures, and an older sister had had minor disorders of consciousness which stopped spontaneously at 15 years of age.

Electroencephalographic Findings.—The interseizure record (fig. 3*A*) of the affected twin, M. W., was normal. A record obtained during a seizure showed high voltage paroxysmal fast activity during the seizure and excessive slow activity before and after the seizure. The record (fig. 3*B*) of the unaffected twin, I. W., was similar to the interseizure record of her twin and was normal.

All criteria indicated that the twins were monozygotic.

Pair Analysis.—These girls were monozygotic twins, one normal, the other with cryptogenic grand mal seizures. A family history of seizures was obtained. Electroencephalographic findings were normal and similar, except for the record obtained during a seizure in the affected twin.

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7. The clinical information on this pair was supplied through the courtesy of Dr. R. R. Patterson, Birmingham, Ala.

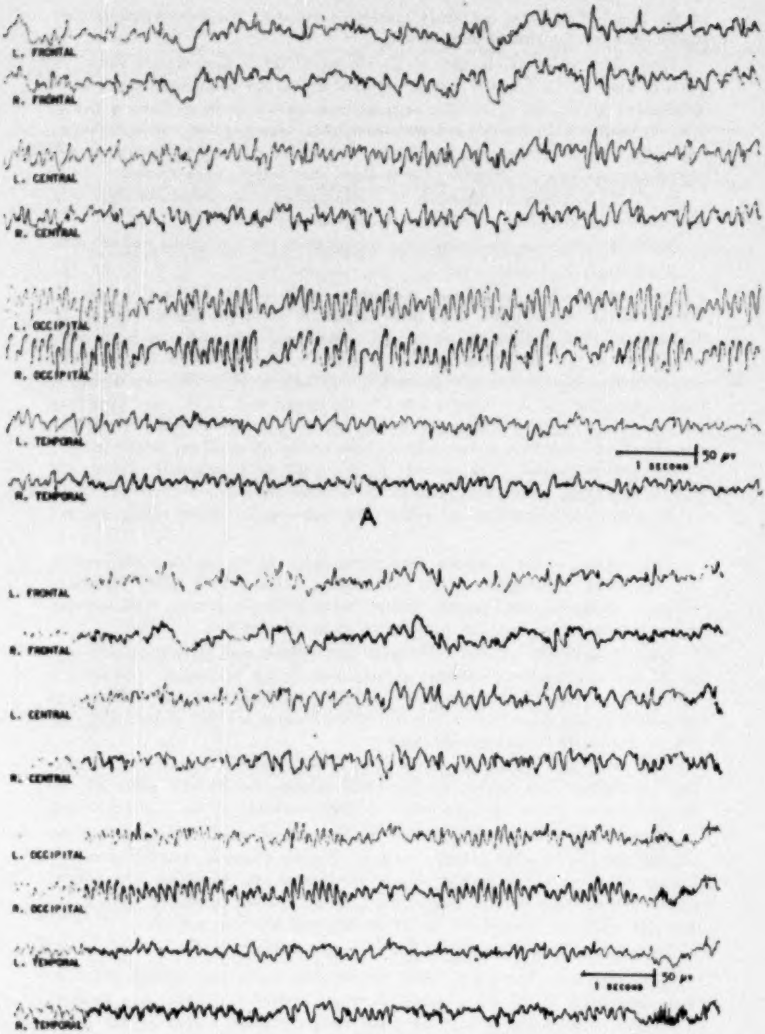


Fig. 3 (twin pair 3).—Electroencephalograms of monozygotic twin girls, aged 7 years. *A*, made Jan. 3, 1948, is the interseizure record of M. W. who had had grand mal seizures since the age of 2 years. *B*, made Feb. 11, 1948, is a normal electroencephalogram of I. W. who had no seizures and no febrile convulsions.

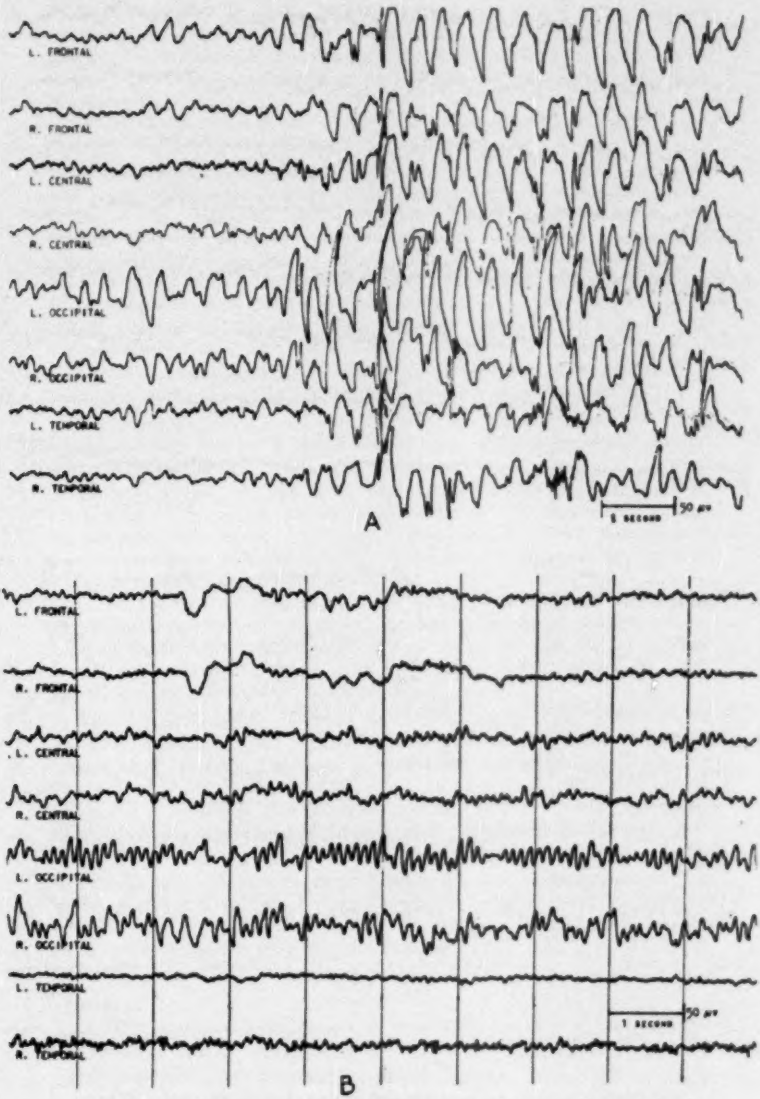
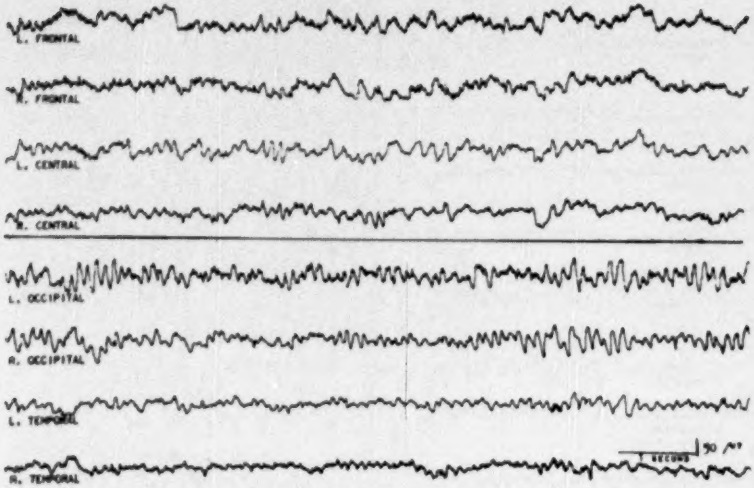


Fig. 4 (twin pair 4).—Electroencephalograms made May 10, 1949 of dizygotic twin girls 6 years of age. *A* is of J. D. who had had grand mal seizures since the age of 11 months. She was similar to her twin but differed in height, weight, fingerprints and blood type. *B* is of G. D. who had no seizures and no febrile convulsions.



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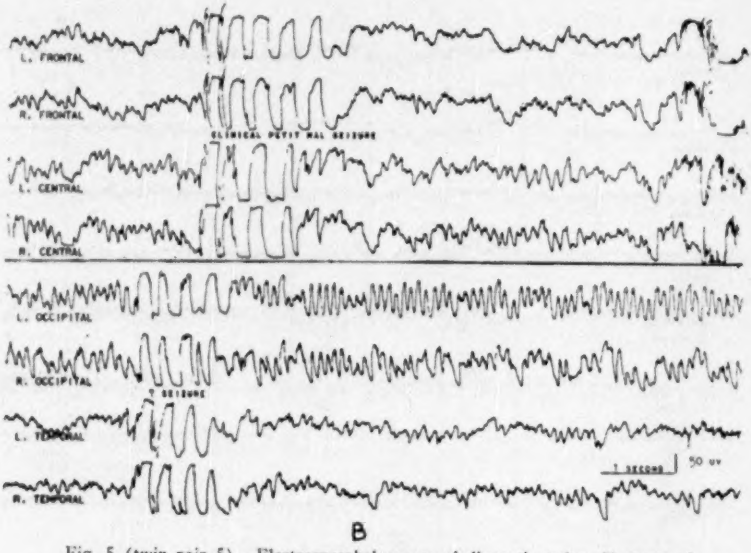

B

Fig. 5 (twin pair 5).—Electroencephalograms of dizygotic twins, 11 years of age. *A*, made June 4, 1949, is of L. W. (girl) who had had grand mal seizures since she was 3 years old and showed signs of mental deterioration. *B*, made June 14, 1949, is of L. W. (boy) who had undetected seizures until their occurrence was noted in the electroencephalographic laboratory.

TWIN PAIR 4.—J. D. and G. D. were dizygotic twin girls, 6 years old. J. D. had had about two generalized grand mal seizures per year since the age of 11 months. The circumstances of birth were unknown. There was no history of trauma to or infection of the central nervous system. Results of the neurologic examination were normal.

G. D., the co-twin, had had no disorders of consciousness at any time, and there was no family history of disorders of consciousness.

Electroencephalographic Findings.—The record (fig. 4*A*) of J. D., the twin with grand mal seizures, showed bursts of high voltage 3 per second waves, with occasional wave and spike formation, somewhat more pronounced in the left occipital area. The appearance of these paroxysmal rhythms was not associated with any disorder of consciousness. Hyperventilation produced a moderate build-up. The record (fig. 4*B*) of the unaffected twin, G. D., showed 9 per second activity in the occipital regions, and on the right this was mixed with medium to high voltage 4 to 5 per second waves. Hyperventilation produced a big build-up, with the appearance of many high voltage 2 per second waves.

The twins were strikingly similar in appearance but were slightly different in height and weight. The blood groups and fingerprints were dissimilar.

Pair Analysis.—These twins were dizygotic, one clinically normal, the other with grand mal seizures of undetermined origin. The electroencephalographic findings were dissimilar.

TWIN PAIR 5.—L. W. and L. W. were female and male dizygotic twins, 11 years of age. L. W., the girl, had had generalized grand mal seizures with increasing frequency since the age of 3 years. There was only partial relief obtained from anticonvulsant medication, and she showed evidence of mental deterioration. Results of neurologic examination were normal.

L. W., the boy, was considered by the family to be free from disorders of consciousness. During the electroencephalographic study, clinical petit mal attacks occurred at the time of petit mal patterns in the record. The mother had had severe "sick headaches" associated with the menses. An older sister had grand mal seizures and was mentally deteriorated.

Electroencephalographic Findings.—The record (fig. 5*A*) of L. W., the girl with grand mal seizures, was abnormally and diffusely slow but showed no specific "epileptogenic" patterns. There was no build-up on hyperventilation. The record (fig. 5*B*) of the male co-twin, L. W., who was thought to be normal, showed paroxysmal 3 per second wave and spike patterns, especially during hyperventilation. In addition, paroxysmal 25 to 30 per second activity appeared from time to time.

Pair Analysis.—These were dizygotic twins, one with grand mal seizures and mental deterioration and the other with previously undetected petit mal seizures. There was a family history of seizures. Electroencephalographic findings were dissimilar but compatible with the clinical findings in each child.

COMMENT

In this series of twin pairs the variable influences of heredity and environment in the production of convulsive disorders can be observed. In the 2 dizygotic pairs inheritance was dissimilar. In the pair having a family history of epilepsy both twins had seizures and cerebral dysrhythmia but of different types. In the pair without a family history

of epilepsy only one had cerebral dysrhythmia and seizures, and the type of dysrhythmia suggested that the disorder may be "symptomatic."

In the 3 monozygotic pairs inheritance was identical. Only one member of each pair had seizures. In pair 1 there was no family history of seizures and the influence of heredity was negligible, as the affected twin's seizures appeared to be the result of acquired brain disease. In pairs 2 and 3 there was a family history of epilepsy, and the electroencephalographic findings were similar in each pair. It seems quite possible that the unaffected twin of pair 3 may yet have seizures as she is only 8 years old, but in pair 2 the tendency to seizures of the unaffected twin (as manifested by a definite cerebral dysrhythmia) may continue to remain below the clinical threshold as it has for twenty-four years. It should be pointed out that the convulsive disorder in the affected members of pairs 2 and 3 was relatively mild, and this may account for the lack of clinical seizures in the co-twins in each case.

The results from the analysis of this small series confirm the previously expressed opinion that epilepsy and cerebral dysrhythmia may be either inherited or acquired. An inherited predisposition to epilepsy, as manifested by cerebral dysrhythmia, is not necessarily synonymous with clinical seizures. The usefulness of electroencephalographic studies in determining the presence or absence of hereditary factors in the causation of epilepsy is confirmed by this study.

SUMMARY

1. Clinical and electroencephalographic findings are reported in 5 twin pairs in which one or both twins had a convulsive disorder.

2. If an inherited tendency to have seizures (as manifested by cerebral dysrhythmia) is mild, even identical inheritance (as in monozygotic twins) of cerebral dysrhythmia is not synonymous with the development of clinical seizures. If the inherited tendency is great, dysrhythmia and clinical seizures may be found even in the presence of dissimilar inheritance (as in dizygotic twins).

3. Electroencephalography is a useful means with which to evaluate the degree of influence hereditary factors exert in the production of clinical convulsive disorders.

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BRONCHOPULMONARY MYCOSIS

Simultaneous Primary Occurrence in Four Children and Their Mother with Subsequent Healing by Diffuse Miliary Calcification; a Twelve Year Observation

BRENTON M. HAMIL, M.D.
DETROIT

THE IMPORTANCE of fungi as causes of pathologic changes in the lungs associated with acute and chronic respiratory illnesses is generally recognized. Their relation to pulmonary calcification not proved to be tuberculosis is an important and disputed question.[1] The fewness of cases of pulmonary mycoses reported in children, especially within family groups, justifies presenting the record of 5 cases of bronchopulmonary mycosis in a single family.

REVIEW OF THE LITERATURE

Bennett,[2] in 1840, was the first to investigate and describe pneumonomycoses. Schnyter,[3] in 1847, described mold infection in the lungs. In 1855, Virchow [4] gave the name pneumonomycosis to the disease. With 3 cases of chronic pulmonary disease Virchow [4] demonstrated at postmortem examination Aspergillus fumigatus, which in his opinion was responsible for the pathologic changes.

The early interest in the subject is evidenced by the report of Reubold [5] in 1854, disproving Berg's [6] original observations that the

From the Department of Pediatrics, Henry Ford Hospital.

1. (*a*) McLeod, J. H.; Emmons, C. W.; Ross, S., and Burke, F. G.: Histoplasmosis: A Report of Four Cases, Two in Siblings; Histoplasmin Test and Other Diagnostic Procedures, J. Pediat. **28**:275 (March) 1946. (*b*) Christie, A., and Peterson, J. C.: Histoplasmin Sensitivity, ibid. **29**:417 (Oct.) 1946. (*c*) Christie, A., and Peterson, J. C.: Pulmonary Calcification and Sensitivity to Histoplasmin, Tuberculin and Haplosporangin, J. A. M. A. **131**:658 (June 22) 1946. (*d*) Sontag, L. W., and Allen, J. E.: Lung Calcifications and Histoplasmin-Tuberculin Skin Sensitivity, J. Pediat. **30**:657 (June) 1947. (*e*) Emmons, C. W.; Olson, B. J., and Eldridge, W. W.: Studies of the Role of Fungi in Pulmonary Disease: I. Cross Reactions of Histoplasmin, Pub. Health Rep. **60**:1383 (Nov. 23) 1945.

2. Bennett, J. H.: On the Parasitic Fungi Found Growing in Living Animals, Tr. Roy. Soc. Edinburgh, 1840-1844, vol. 15; Edinburgh, Neill & Co., 1862.

3. Cited by Törnell.[21]

4. Virchow, R.: Beiträge zur Lehre von den beim Menschen vorkommenden pflanzlichen Parasiten, Virchows Arch. f. path. Anat. **9**:557, 1855; cited by Craven.[28]

5. Reubold, W.: Beiträge zur Lehre vom Soor, Berlin, G. Reimer, 1854.

6. Berg, F. T.: Om torsk hos barn [Thrush in Children], Stockholm, L. J. Hjerta, 1846.

infectious agent of mycotic diseases attacked only stratified epithelium, and by Uhle and Wagner's [7] demonstration as early as 1868 that Monilia albicans may affect internal organs. Rénon,[8] in 1897, published a complete monograph which included experimental, as well as clinical, observations.

Classification.—Castellani was the first to describe bronchomoniliasis (1905) as a disease entity, with the report of a disorder clinically indistinguishable from pulmonary tuberculosis as observed among the tea tasters in Ceylon.[9] His continued interest led to the establishment of a formidable classification of the yeastlike fungi and rigid criteria for the separate identification of pathogenic versus nonpathogenic species and varieties.[10] Castellani [11] classified the fungi which may produce lesions simulating tuberculosis as follows:

1. "Yeastlike" fungi:
   - Blastomyces
   - Cryptococcus (Torula)
   - Saccharomyces
   - Monilia (Candida)
   - Endomyces
2. Filamentous fungi
   - a. Slender type
     - Nocardia (Actinomyces)
     - Anaeromyces
     - Vibriothrix
   - b. Larger type
     - Oidium (Candida)
     - Hemispora
   - c. Types with characteristic conidial structures and fructification
     - Aspergillus
     - Penicillium

7. Uhle, J. P., and Wagner, E.: Handbuch der allgemeinen Pathologie, ed. 4, Leipzig, O. Wigand, 1868, vol. 12, p. 596.

8. Rénon, L.: Étude sur l'aspergillose chez les animaux et chez l'homme, Paris, Masson & Cie, 1897.

9. Castellani, A.: Observations on "Tropical Broncho-Oidiosis," Brit. M. J. **2**:868, 1910. Castellani, A.; Douglas, M., and Thomson, T.: Notes on Certain Forms of Bronchitis Clinically Resembling Tuberculosis: Bronchohemisporosis, Bronchomoniliasis, Bronchoanaeromycosis, J. Trop. Med. **24**:149 (June 1) 1921.

10. (*a*) Castellani, A.; Douglas, M., and Thomson, T.: Mixed Mycotic Infections of the Bronchi: The Mixed Monilia and Anaeromyces Infection, J. Trop. Med. **28**:257 (July 15) 1925. (*b*) Castellani, A.: A Short General Account for Medical Men of the Genus Monilia: Persoon, 1797; Em. Bonorden, 1851; Vuillemin, 1911; Castellani and Chalmers, 1919; Pollacci and Nannizzi, 1927, ibid. **40**:293 (Dec. 1) 1937.

11. Castellani, A.: Certain Bronchomycoses Which May Simulate Pulmonary Tuberculosis, J. Trop. Med. **32**:1 (Jan. 1); 17 (Jan. 15) 1929.

Mucor
Rhizomucor
Acrimoniella
Sporotrichum
Acladium

Identification was established by cultural growth and microscopic characteristics. His classification of different varieties of Monilia [12] was based chiefly on the fermentative reactions in the following carbohydrates: glucose, levulose, maltose, galactose, sucrose (saccharose), lactose and inulin. He presented two tables for the identification and classification, and a key to the identification of the principal species was given.

A serologic classification was established by reactions to agglutination and complement fixation tests, placing most Monilia pathogenic for man in four serologic groups.[10b]

Group	Type
1	Monilia pinoyi, Monilia metalondinensis, Monilia tropicalis and their varieties
2	Monilia macedoniensis, Monilia macedoniensoides, Monilia chalmersi and Monilia parachalmersi
3	Monilia pseudotropicalis, with its varieties
4	Monilia krusei

The serologic groups 1, 2 and 4 were said to be well defined and the differentiation was clearcut. A recheck of the biochemical characteristics of six of these original strains of Monilia showed that these species remained constant in their biochemical characteristics for periods varying from twenty to twenty-seven years.[13]

Nomenclature.—In recent literature the generic name Monilia has been replaced by mycologists with the name Candida [14]; just as the original name Oidium albicans used by Castellani [15] was changed to Monilia albicans, it now becomes Candida albicans. In the following discussion

12. (*a*) Castellani.[10b] (*b*) Castellani.[11] (*c*) Castellani, A., and Chalmers, A. J.: Manual of Tropical Medicine, ed. 3, William Wood & Company, 1919, vol. 3, pp. 1093-1094.

13. Swartzwelder, J. C.: The Permanence of the Biochemical Characters Used in the Differentiation of Certain Species of Fungi, J. Trop. Med. **40**:246 (Oct. 15) 1937.

14. Keeney, E. L.: Sodium Caprylatei: New and Effective Treatment for Moniliasis of the Skin and Mucous Membranes, Bull. Johns Hopkins Hosp. **78**: 333 (June) 1946. Hiatt, J. S., Jr., and Martin, D. S.: Recovery from Pulmonary Moniliasis Following Serum Therapy, J. A. M. A. **130**:205 (Jan. 26) 1946.

15. Castellani, A.: Hæmorrhagic Bronchitis of Non-Tubercular Origin, in Conference in Health Problems in Tropical America, Boston, United Fruit Company, 1924, p. 487; Tr. M. Soc., London **45**:63, 1923. Footnote 9.

the terminology used by Castellani is employed, inasmuch as his classification [13r] was applied in identifying the organisms and all but the most recent reports in the literature use this system.

Monilia pinoyi, the organism identified repeatedly in the cases to be reported here, heads the list in serologic group 1 and is given as a frequent cause of primary bronchomoniliasis. Castellani and his associates also reported the existence of true Monilia and Anaeromyces infections in which each of the two organisms played an important role.[10a] It is quite apparent that the Aspergillus, as well as the Monilia, cultured from the sputums and bronchoscopic material obtained from the patients in this study was similarly of pathogenic importance, as reported in 1 case by Reed.[16]

The bronchomycoses most frequently reported in medical literature are moniliasis and aspergillosis. According to the classification of Castellani, Aspergillus fungi are members of the filamentous group. They are common in nature and, of approximately 350 named in the literature, Thom and Raper [17] accepted 89 species, varieties and mutations, which they presented in 13 groups. Aspergillus niger and Aspergillus fumigatus groups were definitely stated to have primary pathogenicity for man.

Criteria for Diagnosis.—Cases of bronchomoniliasis or pulmonary aspergillosis in the literature are presented with extreme care on the part of reviewers to substantiate their clinical observation and diagnosis with as many of the criteria gathered from the literature as possible for the unqualified laboratory proof of the pathogenicity of the organisms isolated. Numerous cases of chronic pulmonary conditions have been reported, and the subject from a clinical point of view is somewhat confused by the variety of classifications used by mycologists and the various criteria for diagnosis based on roentgenologists' interpretations of roentgenograms. The majority of cases reported are of middle-aged and older people. Consequently, bronchomycosis has been considered a disease of adults.

The subject of pulmonary moniliasis was discussed by Bakst, Hazard and Foley [18] in 1934, in an article accompanied with an extensive bibliography. Little has been added to the understanding of this disease since that time. Díaz Rivera,[19] in 1941, analyzed the 23 cases reported in the

16. Reed, J. A.: Aspergillosis and Moniliasis: Case Report with Necropsy Findings, South. M. J. **28**:729 (Aug.) 1935.

17. Thom, C., and Raper, K. B.: A Manual of the Aspergilli, Baltimore, Williams & Wilkins Company, 1945, pp. 92 and 286.

18. Bakst, H. J.; Hazard, J. B., and Foley, J. A.: Pulmonary Moniliasis, J. A. M. A. **102**:1208 (April 14) 1934.

19. Díaz Rivera, R. S.: Bronchomoniliasis: A Critical Review, Bol. Asoc. méd. de Puerto Rico **33**:107 (March) 1941.

literature by nine American authors and presented many interesting data in a critical review of the subject. The youngest patient was 15 years old and had been ill about two years. The mean age of 36.9 years seemed to confirm the opinion that bronchomoniliasis is a disease of adults.

Koerth, Donaldson and McCorkle [20] reviewed the literature at about the same time and concluded that there was little agreement on the requirements necessary to a diagnosis of bronchomoniliasis. Many investigators have contended that pathogenicity for laboratory animals is not necessary to prove the virulence for man of an organism isolated from sputum, but many others have accepted this as essential, owing to the constant caution in the literature to avoid confusion in diagnosis with tuberculosis.[21] Recent reports of other cases [22] have helped little in the solution of the difficult problems of conclusive diagnosis, specific pathology and clinical management of the condition.

Lapham,[23] in 1926, advanced the thesis that in many cases of primary infection of the lungs with Aspergillus fumigatus a diagnosis of tuberculosis is made but is not proved. She presented 10 cases of aspergillosis collected from an obscure village in the Blue Ridge Mountains and classified the disease as wet, or parenchymatous, and dry, or interstitial. The paper was discussed by Castellani, of New Orleans, who classified aspergillar mycosis the same as any other mycosis, into primary and secondary types. The aspergilli observed in cases of tuberculosis are, as a rule secondary invaders; but the primary type of Aspergillus bronchomycosis exists in geographic and occupational distribution as reported by Castellani and others. He also called attention to primary Monilia bronchomycosis and the clinical and roentgenographic resemblance of both mycoses to tuberculosis.

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20. Koerth, C. J.; Donaldson, J. M., Jr., and McCorkle, R. G.: Bronchomoniliasis, Am. Rev. Tuberc. **43**:723 (June) 1941.

21. Törnell, E.: Thresher's Lung: Fungoid Disease Resembling Tuberculosis or Morbus Schaumann, Acta med. Scandinav. **125**:191, 1946.

22. Baltzan, D. M.: Bronchomoniliasis in Saskatchewan, Canad. M. A. J. **43**:224 (Sept.) 1940. Wiese, E. R., and Bixby, E. W.: Bronchiectasis Associated with Monilia Simulating Pulmonary Tuberculosis, J. Lab. & Clin. Med. **26**:624 (Jan.) 1941. Farrell, W. A.: Bronchomoniliasis, Canad. M. A. J. **48**:28 (Jan.) 1943. McCollum, J. K.: Pulmonary Moniliasis with Primary Bronchogenic Pneumonia, Lancet **2**:306 (Sept. 13) 1941. Wylie, P. E., and De Blase, J. A.: Bronchopulmonary Moniliasis, J. A. M. A. **125**:463 (June 17) 1944. Kostmann, R.: Moniliasis of the Respiratory Tract, Acta pædiat. **32**:520, 1945; Bronchomoniliasis, Nord. med. (Hygiea) **27**:1586 (Aug. 10) 1945. Nevius, W. B.: Bronchopulmonary Moniliasis, Brooklyn Hosp. J. **6**:8 (Jan.) 1948.

23. Lapham, M. E.: Aspergillosis of the Lungs and Its Association with Tuberculosis, J. A. M. A. **87**:1031 (Sept. 25) 1926.

Hamman,[24] in a paper presented in 1927, asserted that mycotic disease of the lung does not present a distinct clinical picture but masquerades in the likeness of any of a number of well known pulmonary afflictions, making a searching investigation necessary for its identification. He characterized the clinical features with the terse statement that "fungus infection should always be suspected when there is pulmonary disease that does not readily and easily fit into one of the accepted diagnostic categories."

Craven [25] in 1935, and Van Ordstrand,[26] in 1940, reviewed the literature concerning pulmonary aspergillosis, and other authors [27] have presented additional cases. Wahl,[28] in 1936, discussed under the general subject of pneumonomycoses 6 cases, from 4 of which Aspergillus was cultured. He declared that early diagnosis is essential for cure. Vadala,[29] in 1940, emphasized the value of bronchoscopic aspiration of exudate for culture of the pathogenic fungus. Reeves,[30] in 1941, analyzed the pertinent data in 79 cases of bronchomycosis, giving particular attention to early, as well as late, roentgenographic changes in the lung from blastomycosis (16 cases), actinomycosis (10 cases), moniliasis (40 cases), sporotrichosis (3 cases), aspergillosis (5 cases) and others (5 cases). The 40 patients with bronchomoniliasis ranged in age from 4 months to 65 years and had had symptoms from one month to five years; 24 had parenchymal involvement and 16 were living. The 5 patients with aspergillosis ranged in age from 26 to 47 years; symptoms had been present from four months to one year; 3 had parenchymal involvement; 3 were living. Reeves's report appears to indicate the relative incidence of infection by different species of pathogenic fungi in bronchopulmonary mycoses and the age distribution and morbidity in one locality.

The rigid criteria for the diagnosis of primary bronchomycosis have been emphasized. Generally, diagnosis depends primarily on discovery

24. Hamman, L.: Clinical Manifestations of Pneumonomycosis, Am. Rev. Tuberc. **16**:575 (Nov.) 1927.

25. Craven, E. B., Jr.: The Rôle of Aspergilli and of Moniliae in Chronic Non-Tuberculous Pulmonary Disease, With and Without Asthma, South. Med. & Surg. **97**:678 (Dec.) 1935.

26. Van Ordstrand, H. S.: Pulmonary Aspergillosis, with Report of Case, Cleveland Clin. Quart. **7**:66 (Jan.) 1940.

27. Donaldson, J. M., Jr.; Koerth, C. J., and McCorkle, R. G.: Pulmonary Aspergillosis, J. Lab. & Clin. Med. **27**:740 (March) 1942. Coe, G. C.: Primary Bronchopulmonary Aspergillosis: An Occupational Disease, Ann. Int. Med. **23**: 423 (Sept.) 1945.

28. Wahl, E. F.: Pneumomycosis, Tr. Am. Therap. Soc. **36**:35, 1936.

29. Vadala, A. J.: Mycotic Infection of the Bronchopulmonary Tract, Ann. Otol., Rhin. & Laryng. **49**:291 (June) 1940.

30. Reeves, R. J.: The Incidence of Bronchomycosis in the South, Am. J. Roentgenol. **45**:513 (April) 1941.

of the suspected organism in the sputum. In collecting specimens for culture, precautions should be taken to obtain sputum coughed up from the lower part of the respiratory tract. Cultural characteristics should classify the organism as one probably pathogenic for man. Of the numerous species of Aspergillus, only Aspergillus fumigatus and Aspergillus niger are considered capable of producing pathogenic changes in human tissues.[17]

With Monilia, whether the organism is isolated in the form of yeast-like cells or as mycelia, it should show definite cultural characteristics.[12e] Typical colonies should be produced on Sabouraud's medium; the organism should ferment dextrose, levulose and maltose, with the production of gas. If the Castellani [12] criteria for classification are followed, the organism should fall into one of the serologic groups considered pathogenic for man. According to Benham,[31] strains of Monilia from oral thrush, intestinal sprue and moniliasis of the skin have appeared to be identical, and this type is referred to as Monilia albicans. This organism is also considered to be the causative agent of bronchomoniliasis and is referred to in recent literature as Candida albicans.[14]

In describing the organism, Benham [31] stated:

> Monilia albicans produces a definite mycelium made up of elongated cells which do not readily fall apart, produced by buds which accumulate in dense ball-like clusters along the mycelial threads. Globular, thick-walled chlamydospores are formed, no ascospores. An "inverted pine tree" forms in a gelatin stab. Ferments regularly dextrose, levulose, and maltose with the production of acid and gas. Varies in the reaction of galactose and saccharose. Giant colony, smooth and pasty at first, later convoluted at center, often showing craters of ruptured gas bubbles. Agglutinates readily in serum produced against a known strain of Monilia albicans. Some cross-agglutination with other species, but readily separated from these by agglutinin absorption. Agglutinates to full titre in serum prepared against Monilia candida. Absorption not yet determined. Pathogenic for rabbits.

Pathogenicity.—As stated previously, the demonstration of pathogenicity of isolated organisms for laboratory animals as proof of virulence for man has been debated by various investigators. The literature shows little agreement on the determinants necessary for a diagnosis of bronchomycosis. This confusion seemingly results from attempts to use the same criteria for positive diagnoses in long-existing chronic pulmonary conditions, in which the fungus may be a secondary pathogen, and in primary bronchomycoses, in which the onset of symptoms presents a more or less classic clinical picture of acute and subacute pulmonary illness. In Castellani's opinion,[32] a diagnosis of bronchomoniliasis was

31. Benham, R. W.: Monilias, Yeasts and Cryptococci: Their Pathogenicity, Classification and Identification, Am. J. Pub. Health **22**:502 (May) 1932.

32. Castellani, A.: Internal Mycoses, M. Clin. North America **11**:1123 (March) 1928.

justifiable only when there were continuous absence of tubercle bacilli and the constant presence of Monilia in the sputum. Although Monilia isolated from sputum may have caused the death of rabbits when injected intravenously or intraperitoneally, resulting in septicemia, he did not consider this proof, necessarily, that the organism was a pathogen causing bronchomoniliasis unless the lesions which he stated to be pathognomonic were produced when the organisms were injected intrapulmonarily.[33] His group also showed that the virulence of different specimens of the same species of Monilia may vary, as well as that of different species, and that Monilia with the same biochemical properties may differ greatly in their pathogenicity for man and laboratory animals.[10a]

Koerth, Donaldson and McCorkle,[20] after an extensive review of the literature, concluded that their inability to prove pathogenicity for laboratory animals of the organism isolated from the sputum of either of 2 patients was not sufficient reason to question the diagnosis in either of them. The blood of 1 patient produced the agglutination of the organism, and the reaction on skin test with vaccine was positive for the other patient. Their conclusion, agreeing with that of other writers,[34] seems a logical one: When all other etiologic factors are ruled out and a Monilia, or other fungus considered to be pathogenic, consistently present in the sputum is capable of producing a positive cutaneous reaction in the patient, when suspensions of the fungus are agglutinated by the patient's blood serum and when the patient's serum shows a strong complement fixation reaction for the organism, then it is not necessary to demonstrate pathogenicity for laboratory animals to prove the organism to be the etiologic agent. If bronchoscopic examination reveals a definite inflammatory process in the bronchial mucosa, and secretions swabbed from the lesions produce growth of pathogenic type fungi, animal inoculation should not be necessary, although it is desirable, except to rule out the presence of tuberculosis.

Signs and Symptoms.—The literature records few hematologic observations [10] in bronchomycoses. Anemia has been seen consistently, but definite changes from normal in the total or differential white blood cell counts have not been found. Some elevation of the sedimentation rate has been reported, but few reports are on record. Lack of these data indicates failure to obtain definite diagnostic information during the acute initial stage of the disease.

The sputum, when it is copiously produced in the acute stages, has a characteristic yeasty odor, and in both aspergillosis and moniliasis it

33. Castellani, A.: Notes on Certain Bronchomycoses Which May Simulate Pulmonary Tuberculosis, Am. Rev. Tuberc. **16**:541 (Nov.) 1927.

34. Flinn, R. S., and Flinn, J. W.: Bronchomoniliasis, J. Trop. Med. **40**:237 (Oct. 15) 1937.

has a granular appearance, seeming "pearly" or "gruel-like" in the sputum cup. The odor is distinctly sweetish and yeasty.

The roentgenologic picture in both pulmonary aspergillosis and moniliasis may be indistinguishable from that in tuberculosis.[35] The lesions frequently present a miliary distribution, scattered from bases to apexes, but more heavily concentrated in the bases and midportion of the lungs with almost complete absence from the extreme apexes, a picture which is in contrast to the usual finding in hematogenous tuberculosis. These scattered lesions usually present a soft, fluffy appearance, with a fuzziness to the borders in the acute and subacute stages. There is no evidence of frank cavitation; the hilar areas are accentuated, and the interlobar pleura may be thickened. As healing progresses, the lesions become more dense and fibrotic and show various degrees of deposition of calcium salts. Long-continued, arrested but unhealed, chronic conditions show extensive fibrotic changes.

Symptoms, as a rule, have been classified according to degree—mild, moderate and severe.[36] There are certainly different stages in the course of bronchopulmonary mycoses, depending on the type and intensity of management, namely, acute, subacute and chronic. The source of infection is in nature, where the organism leads a parasitic life on plants or a saprophytic existence on plants or in the soil. Little is known of this phase of medical mycology. The mode of infection is a matter of conjecture,[37] but it is likely that the route is by inhalation. Farah [36c] stated that "although it may be transmitted from man to man, probably as a saprophyte living in nature, growing, for instance, on decomposing wood, dead leaves and fruit, it becomes pathogenic." It is difficult, however, to produce the disease in animals except by intratracheal or intrapulmonary injection. The organisms can be carried in the blood vessels and lymphatics [37a] and have produced endocarditis, meningitis and abscesses of the brain and spinal cord.[38] Smith [37a] stated

35. (*a*) Carter, R. A.: Pulmonary Mycotic Infections, Radiology **26**:551 (May) 1936. (*b*) Doub, J. P.: Roentgenologic Aspects of Bronchomycosis, ibid. **34**:267 (March) 1940.

36. (*a*) Koerth and others.[20] (*b*) Ikeda, K.: Bronchopulmonary Moniliasis: Its Relation to Obscure Chronic Pulmonary Infection, Arch. Path. **22**:62 (July) 1936. (*c*) Farah, N.: Observations on Castellani's Bronchomoniliasis, with Report of a Case with Pneumonic Onset and a Peculiar Clinical Course, J. Trop. Med. **26**:1 (Jan. 1) 1923.

37. (*a*) Smith, D. T.: Diseases Due to Fungi, in Blumer, G.: The Therapeutics of Internal Diseases, New York, D. Appleton-Century Company, Inc., 1941, vol. 3, pp. 1-75. (*b*) Ikeda.[36b]

38. Anderson, G. C.: Fungous Infections of the Brain: Report of Four Cases, Arch. Surg. **42**:379 (Feb.) 1941. Joachim, H., and Polayes, S. H.: Subacute Endocarditis and Systemic Mycosis (Monilia), J. A. M. A. **115**:205 (July 20) 1940.

that, with few exceptions (skin), the fungi rarely, if ever, spread from one patient to another. The possibility of transmission from person to person is mentioned in the literature, but no better proof is given than the occurrence of the disease in 3 members of the same family.[38]

Differential Diagnosis.—The differential roentgenologic diagnosis is confused by the similarity of various pathologic changes caused by acute and chronic inflammatory processes, but attempts have been made to differentiate the roentgenologic findings in various bronchopulmonary mycoses.[35] Pulmonary mycotic infections have so much in common that only mycosis in general may be suspected from roentgenograms. There are no findings which are pathognomonic and the signs usually are so similar to those of tuberculosis, both clinically and pathologically, that a positive diagnosis can be made only by identification of the organism. Carter [35a] was of the opinion that, since all pulmonary infections cannot have exhaustive bacteriologic study, the benefit of successful early treatment is contingent on alertness to suspicious but not distinguishing features which may single out cases for such investigation. In differential diagnosis of pulmonary mycoses, one must consider coccidioidal granuloma, blastomycosis, actinomycosis, streptothricosis, torulosis, moniliasis, aspergillosis, penicilliosis and mucor mycosis.[39] Unfortunately, roentgenologic detail is not stressed in the literature, but, generally speaking, the roentgenographic appearance described for both moniliasis and aspergillosis is that of a fine mottling throughout both pulmonary fields, the apexes being clear, with a considerable amount of emphysema, superseded by a generalized fibrosis as the condition improves, or associated with fibrous rings walling off small densities or surrounding calcified nodules with condensation of calcium as healing progresses.

Attention has been repeatedly directed to miliary calcification of the lung from an unknown cause.[40] The presence of nontuberculous pulmonary calcification with an associated positive reaction to a histoplasmin intradermal test necessitates more intensive search for a specific mycotic cause of the healed, calcified pulmonary lesions.[41] Christie and Peterson,[42] after discussing the results of more than 2,000 histoplasmin tests, concluded that a direct causal relationship between pulmonary

39. (*a*) Footnote 35. (*b*) Fawcitt, R.: Fungoid Conditions of the Lungs, Brit. J. Radiol. **9**:354 (June) 1936.

40. Sayer, R. R., and Meriwether, F. V.: Miliary Lung Disease Due to Unknown Cause, Am. J. Roentgenol. **27**:337 (March) 1932. Sutherland, C. G.: Miliary Calcification in the Lung, M. Clin. North America **8**:1273 (Jan.) 1925.

41. (*a*) Footnote 1. (*b*) Peterson, J. C., and Christie, A.: Histoplasmosis and Pulmonary Calcifications, Am. Rev. Tuberc. **47**:361 (April) 1948.

42. Christie and Peterson.[1b] Peterson and Christie.[41b]

calcification and histoplasmosis has not been proved. Histoplasmin sensitivity may merely be an index of the over-all problem of pulmonary and systemic mycotic infection.[43]

Pathologic Aspects.—The pathologic tissue changes observed in such autopsy material as has been studied include no lesions which may be considered specific in bronchopulmonary moniliasis or aspergillosis. Early primary lesions have not been described and probably cannot be distinguished from those caused by any other form of inflammation.[20] Since fungi require an acid medium for growth, it has been postulated that necessarily there must be some chemical change in the otherwise alkaline secretions of the respiratory tract to favor continued growth of the organisms. This suggests the presence of a preexisting primary lesion which must alter the chemical reaction of the tissues before the invasion of fungi can occur.[36b] Although these fungi normally are relatively nonvirulent for man under conditions favorable to unrestrained growth, they may become pathogenic, with potentialities of systemic dissemination.[44] It is likely that tissue sensitization, as in tuberculosis,[45] is a requirement for widespread pulmonary or systemic dissemination.

Autopsy studies of patients for whom disease fungi have been indisputably proved to be the cause of death are rare, although autopsy reports have been published by various observers.[46] The gross and microscopic pathologic changes closely resembled those of pulmonary tuberculosis, with consolidation, cavitation, fibrosis and tubercle formation.[20] Tubercles were composed of a caseous center surrounded by epithelioid cells, lymphocytes and an occasional giant cell. Lewis [46g] presented a case in which Monilia was established as a sufficient cause of

43. Emmons and others.[1e] Howell, A., Jr.: Studies of Fungus Antigens: I. Quantitative Studies of Cross-Reactions Between Histoplasmin and Blastomycin in Guinea Pigs, Pub. Health Rep. **62**:631 (May 2) 1947.

44. Flinn and Flinn.[34] Kotkis, A. J.; Wachowiak, M., and Fleisher, M. S.: The Relation of Monilia to Infections of the Upper Air Passage, Arch. Int. Med. **38**:217 (Aug.) 1926.

45. Rich, A. R.: The Pathogenesis of Tuberculosis, Springfield, Ill., Charles C Thomas, Publisher, 1944, pp. 330 and 384. Kurotchkin, T. J., and Lim, C. E.: Experimental Bronchomoniliasis in Sensitized Rabbits, Proc. Soc. Exper. Biol. & Med. **31**:332 (Dec.) 1933. Smith, C. E.; Rosenberger, H. G.; Beard, R. R., and Saito, M. T.: The Use of Coccidioidin, Am. Rev. Tuberc. **57**:330 (April) 1948.

46. (*a*) Reed.[1a] (*b*) Ikeda.[36b] (*c*) Flinn, J. W.; Flinn, R. S., and Flinn, Q. M.: A Study of Nine Cases of Bronchopulmonary Moniliasis, Ann. Int. Med. **9**:42 (July) 1935. (*d*) Warr, O. S.: Bronchomoniliasis: Clinical and Pathological Study, with Report of Illustrative Cases, ibid. **5**:307 (Sept.) 1931. (*e*) Joekes, T., and Simpson, R. H.: Bronchomoniliasis, Lancet **2**:108 (July 21) 1923. (*f*) Mendelson, R. W.: Tropical Bronchopulmonary Mycosis, J. A. M. A. **77**:110 (July 9) 1921. (*g*) Lewis, S. J.: Moniliasis of the Lungs and Stomach: Case Report with Autopsy, Am. J. Clin. Path. **3**:367 (Sept.) 1933.

death, and the pathologic details were considered important.[85a] Monilia ulcers were observed in the stomach and the spleen was fibrotic. The lungs showed apexes free of pathologic modification. Superficial pulmonary tissue was normally crepitant. The lungs were honeycombed with countless small pockets of pus 2 to 3 cm. in diameter, mainly associated with medium and small-sized bronchioles. Monilia was observed in the pus on smear. Areas not showing the pus were principally dense and fibrous. Microscopic examination revealed several types of lesions, depending on the stage of the process:

1. Pseudotubercles consisted of a central area of pus cells and mononuclear cells, with fibroblasts, epithelioid cells, plasma cells and young blood vessels in outer spaces; Monilia were scattered throughout. Few giant cells were seen, and they were atypical.

2. Fibrosis or granulation tissue in various stages was seen, with aggregations of small round cells and plasma cells.

3. Chronic inflammatory changes of various sizes were noticed around the bronchioles, with much fibrosis there and in adjacent pulmonary tissue. Few areas showed pulmonary tissue without chronic inflammatory changes. There was a definite tendency for healing of the pseudotubercles by fibrosis. Calcification was not observed.

Mendelson [46f] presented some of the most impressive pathologic information in the literature. His patients came to necropsy in Bangkok, Siam, as the result of some intercurrent medical cause or other accident. He made cultures of lungs routinely in order to obtain a pathologic picture which might be considered the result of a pure mycotic infection. Many lungs were cultured and sectioned. On cut section, the appearance in lungs representing pure myotic infection much resembled that of tuberculosis. The lung tissue cut with difficulty and the small tubercles, which were in reality mycotic tumors, stood out as promient white masses. No necrosis was observed, and the author's opinion was that the fungi have a stimulating effect on the tissue cells. He was not able to determine whether later there was degeneration with production of local abscess, but in view of the fact that mixed infections of long standing presented the same firm connective tissue tumors, he expressed doubt that they would break down except under the most adverse conditions.

Treatment.—Methods of treatment for bronchomycoses have been as varied as have been the new drugs added to the therapeutic armamentarium. Use of iodides in various forms is established as the most effective treatment. Mendelson [46f] stated his opinion that their effect is to hasten the disorganization and absorption of the mycotic tumors. The success of iodide treatment depends on early administration of

adequate amounts [47] and the trend is toward massive doses.[48] The caution formerly observed in gradually increasing the dosage is unwarranted, since it has been established that the symptoms of intolerance are no more frequent with large than with small doses.[49] The only contraindications are presence of tuberculosis or toxic goiter. Iodine may be administered orally in saturated solution of potassium iodide, by vein as in 10 per cent aqueous solution of sodium iodide or by inhalation of ethyl iodide.[50] Swartz [51] recommended the last as the most effective treatment in bronchomoniliasis and systemic or generalized moniliasis. The ethyl iodide is administered with a nebulizer designed to allow a comfortable mixture of the compound and air, and the inhalation is given every second day to avoid a cumulative effect. Aspergillosis may not respond as promptly to iodide therapy as moniliasis, and the use of an arsenical, such as neoarsphenamine (neosalvarsan®) or oxyphenarsine hydrochloride (mapharsen®), may be more effective.

Other methods of treatment have been employed, with which beneficial results were not proved. Sulfonamide preparations, penicillin and streptomycin have been used,[52] as have intravenous injections of methylrosaniline chloride (gentian violet) and methylene blue, which are hazardous as well as ineffective. High voltage roentgen therapy has been used extensively in the treatment of chronic conditions without demonstable success.[19]

REPORT OF CASES

During a period of twelve years records have been accumulated of the onset and progress of bronchopulmonary mycosis in 4 siblings and their mother, with recovery of all the children and supervention of a fatal accident to the mother.

The 4 children had been known by me for two years before they became acutely ill. They were examined first in 1936 in connection with a health survey of country

47. Díaz Rivera.[19] Fawcitt.[59b]

48. Flinn and Flinn.[34] Flinn and others.[46c]

49. Moore, J. E.: The Modern Treatment of Syphilis, Springfield, Ill., Charles C Thomas, Publisher, 1933, p. 141.

50. (*a*) Swartz, J. H.: Treatment of Fungous Infections with Ethyl Iodide Inhalations, Arch. Dermat. & Syph. **40**:962 (Dec.) 1939; (*b*) Inhalations of Ethyl Iodide in Fungous Infections: Further Studies, ibid. **32**:551 (Oct.) 1935. (*c*) Blumgart, H. L.; Gilligan, D. R., and Swartz, J. H.: Elimination of Ethyl Iodide After Inhalation and Its Relation to Therapeutic Administration, J. Clin. Investigation **9**:635 (Feb.) 1931. (*d*) Swartz, J. H.; Blumgart, H. L., and Altschule, M. D.: Ethyl Iodide Inhalations in the Treatment of Mycotic Infections of the Skin and Allied Conditions, Arch. Dermat. & Syph. **21**:182 (Feb.) 1930.

51. Swartz, J. H.: Elements of Medical Mycology, New York, Grune & Stratton, Inc., 1943.

52. Van Bree, R. S.: Moniliasis: Sulfapyridine Treatment, J. Michigan M. Soc. **40**:197 (March) 1941.

TABLE 1.—*Correlation* of Sedimentation Rate, Blood Count, Roentgenographic Changes and Results on Culture with Progress of Treatment in Patient J. C.†*

Date	Sed. Rate, Mm./Hr.‡ Hematocrit, Cu. Mm.	Hemoglobin, Gm. per 100 Cc.	Red Blood Cells, Millions	White Blood Cells	Polymorphonuclear Neutrophils, %	Polymorphonuclear Eosinophils, %	Lymphocytes Small, %	Lymphocytes Large, %	Monocytes, %	Roentgenographic Appearance	Sputum Culture	Culture of Bronchoscopic Smear
Admitted to hospital inpatient department: Syrup of "calcidrine," 1 dr. 4 times a day; KI, 15 gr. 4 times a day												
3/22/38	57/38	15.6	3.58	11,450	80	1	16	2	1	Feathery densities from apexes to bases		
4/ 5/38	.....	10.1	3.63	21,850	87	7	30	1	5	.....	Monilia	Negative smear
5/23/38	51/42	10.5	4.22	13,300	66	3	20	6	1	Pleura thickened	Aspergillus	No culture
6/ 7/38	5/36	....	....	6,800	67	4	21	2	5	Same	Monilia	
6/22/38	41/37	14.3	4.79	9,900	72	3	13	11	1			
Discharged to outpatient department: KI, 30 gr. 4 times a day												
7/ 9/39	.....	11.0	4.23	6,900	76	..	20	3	1	More discrete; less fluffy		
7/30/38	21/47	13.2	4.50	8,850	60	1	22	7	1	.....	Oidium matalense	
8/27/38	24/46	17.6	4.12	8,000	61	..	25	5	9	Same		
10/15/38	22/48	10.5	4.36	8,450	70	..	22	5	3	Same		
Moved out of area March 25, 1939										More condensed		
Readmitted to hospital inpatient department May 10, 1940: KI, 60 to 120 gr. 3 times a day; NaI, 10 Gm. in 100 cc. of water intravenously daily												
5/13/40	.....	10.8	4.04	7,500	70	2	21	7	..	Condensed		
6/13/40	15/45	12.3	4.15	9,550	66	..	25	9	..	Same		
7/16/40	14/44	11.9	4.33	10,200	75	3	20	2	..	Increase in hilar markings	Monilia	
8/15/40	.....	13.1	4.45	11,550	63	1	32	4	..	Increased fibrosis of nodules	Monilia	
Discharged to outpatient department												
10/15/40	12/43	12.7	4.74	7,550	61	1	29	4	5	Same		
12/10/40	11/46	13.5	4.49	7,900	66	1						
12/19/40	.....	....	....	.....	..	..	19	12	..	Same		
Readmitted to hospital inpatient department Jan. 3, 1941: KI, 60 gr. 3 times a day daily; oxyphenarsine hydrochloride, 25 mg. in 300 cc. of 10% dextrose solution intravenously daily for 7 days											Monilia pinoyi	
1/ 7/41	26/42	13.5	4.31	9,700	73	..	20	2	5	.....	.....	Aspergillus
1/14/41	45/44	14.0	4.77	12,600	76	3	16	4	1	Same		
1/22/41	40/43	11.6	4.10	8,800	71	..	22	2	5			
2/ 5/41	31/42	11.9	4.23	9,750	70	2	15	1	3	Same		
Discharged to outpatient department Feb. 18, 1941												
3/ 7/41	17/42	11.9	....	.....	..	..	..	..	..	.....		
4/30/41	7/42	12.5	4.29	6,750	65	2	25	2	4	Definite calcification of nodules		
Readmitted to hospital inpatient department May 1, 1941: Ethyl iodide, 4 cc. inhalation 5 times a week for 4 weeks												
5/ 5/41	17/43	12.7	4.25	7,650	71	2	20	2	5	Same		
Discharged to outpatient department: Autogenous vaccine—Aspergillus (W. C.) and Monilia (P. C.) in increasing dosage weekly for 50 weeks												
6/20/41	10/38	10.5	4.17	7,200	55	3	30	3	9			
7/23/41	.....	12.0	4.53	7,150	71	2	17	3	7			
8/25/41	.....	12.7	4.49	8,800	63	..	30	5	2	More calcification		
10/ 7/41	4/41	12.7	4.53	10,650	66	..	30	1	3			
Nov. 15, 1941: Aspergillus (W. C.) and Monilia (P. C.) in increasing dosage weekly for 50 weeks												
12/ 6/41	4/46	13.7	4.96	9,650	67	..	15	4	14	Same		
2/20/42	16/44	13.5	4.45	9,200	57	2	29	7	4	Much more calcification		
6/ 6/42	9/46	13.7	4.48	7,700	66	1	26	3	4	Miliary calcifications		
9/12/42	6/48	13.1	4.39	6,950	63	1	23	7	6	Denser		
10/ 3/42	3/48	13.3	4.57	8,600	71	2	19	4	4	Same		
2/26/44	9/42	14.5	4.67	8,900	55	1	28	8	..	Dense discrete calcification		
4/24/47	.....	....	....	.....	..	..	..	..	..	Same		
4/23/49	.....	....	....	.....	..	..	..	..	..	No change		

* This table and the three following it show data on a family group of a mother and 4 minor children who became acutely ill with "flu" type respiratory symptoms during January and February 1938. Symptoms varied in degree, but all were ill at the same time in their farm home. The father and older brother were not ill at this time; but the brother later died of acute atypical pneumonia.

† J. C., a girl born Jan. 24, 1923, was 15 years of age at the onset of illness. She had severe "flu" type symptoms from Jan. 20 to Feb. 20, 1938, with fever, chills, general malaise, weakness, sweating and hard, dry, distressing cough. The mother was similarly ill. Relapse occurred March 7, with continued fever, malaise, sweating, cough and blood-streaked sputum. She was under the care of a country physician who referred her to the hospital.

‡ Wintrobe method.

TABLE 2.—*Correlation of Sedimentation Rate, Blood Count, Roentgenographic Changes and Results on Culture with Progress of Treatment in Patient W. C.**

Date	Sed. Rate, Mm./Hr.† Hematocrit, Cu. Mm.	Hemoglobin, Gm. per 100 Cc.	Red Blood Cells, Millions	White Blood Cells	Polymorphonuclear Neutrophils, %	Polymorphonuclear Eosinophils, %	Lymphocytes Small, %	Lymphocytes Large, %	Monocytes, %	Roentgenologic Appearance	Sputum Culture	Culture of Bronchoscopic Smear
Admitted to hospital inpatient department: Syrup of "calcidrine," 1 dr. 4 times a day; KI, 15 gr. 4 times a day												
3/29/38	43/35	10.2	3.61	14,150	76	2	16	2	1	Feathery densities apexes to bases		
4/ 5/38	.....	10.0	3.50	17,100	80	2	9	5	4	.....	.....	Negative smear
5/23/38	45/39	10.7	3.65	11,850	74	..	20	2	4	Pleura thickened	.....	No culture
6/ 7/38	23/24	....	....	13,100	60	8	25	4	3	Same		
6/22/38	32/27	9.9	3.50	13,700	80	1	17	2	..			
Discharged to outpatient department: KI, 20 gr. 4 times a day												
7/ 9/38	.....	9.0	3.27	13,900	68	1	20	5	6	More discrete; less fluffy		
7/30/38	36/36	10.7	3.72	13,500	70	2	23	4	1			
8/27/38	43/38	10.7	3.73	7,850	72	..	24	2	2	Same		
10/15/38	46/40	9.9	3.96	7,450	60	5	28	5	..	Same		
Moved out of area March 25, 1939												
										More condensed		
Readmitted to hospital inpatient department May 10, 1940: KI, 60 to 120 gr. 5 times a day; NaI, 10 Gm. in 100 cc. of water intravenously daily											Monilia	
5/13/40	.....	9.8	3.76	11,000	71	2	25	1	..	Condensing fibrosis		
6/18/40	37/35	10.0	3.79	11,100	60	1	24	1	5	Same		
7/16/40	36/36	9.8	3.96	14,650	71	2	19	6	2	Fibrosis same	Monilia	
8/15/40	.....	11.2	4.13	7,600	68	1	28	3	..	Large hilar markings; same		
Discharged to outpatient department												
10/15/40	38/36	11.9	4.02	10,250	54	..	36	3	5	Same		
12/10/40	34/41	12.3	4.17	6,650	63	2	28	6	1	Same	Penicillium	Aspergillus
12/23/40	40/40	13.1	4.32	10,350	65	3	26	6	1	Miliary fibrosis	Penicillium	
Readmitted to hospital inpatient department Jan. 3, 1941: KI, 60 gr. 3 times a day daily; oxyphenarsine hydrochloride, 35 mg. in 300 cc. of 10% dextrose solution intravenously daily for 7 days										Beginning calcification		
1/14/41	28/30	12.2	4.28	8,250	69	4	19	7	1	Same		
2/ 8/41	32/39	11.8	4.19	9,100	77	2	20	1	..	Early calcification		
Discharged to outpatient department Feb. 18, 1941												
3/ 7/41	32/39	11.7	....	.....	..	..	17	8	3	Discrete calcification of nodules		
4/30/41	30/39	10.8	3.82	10,250	70	1	..	..	..			
Readmitted to hospital inpatient department May 1, 1941: Ethyl iodide, 4 cc. inhalation 5 times a week for 4 weeks												
6/ 5/41	16/29	11.7	4.36	7,700	59	2	36	3	..	Same		
Discharged to outpatient department: Autogenous vaccine—Aspergillus (W. C.) Monilia (P. C.) in increasing dosage weekly for 50 weeks												
6/20/41	17/36	10.8	4.10	7,250	62	5	25	4	4			
7/28/41	23/39	12.0	4.02	7,900	60	..	38	1	1			
8/25/41	19/40	12.7	4.27	8,900	67	..	28	5	..	Same		
10/ 4/41	22/41	12.7	4.13	9,150	61	3	35	..	1			
Nov. 15, 1941: Aspergillus (W. C.) and Monilia (P. C.) in increasing dosage weekly for 50 weeks												
12/ 6/41	12/37	12.3	4.37	9,450	45	2	43	9	1	Same		
2/13/42	17/40	12.3	4.46	8,800	61	4	26	..	9	Same		
6/ 6/42	15/40	11.6	4.08	6,500	69	2	17	17	5	Same		
9/12/42	18/41	12.7	4.31	5,800	70	..	24	5	1	Condensed miliary calcifications		
10/ 3/42	4/43	12.7	4.18	4,700	54	3	36	5	2	More dense, discrete calcification		
3/13/44	10/42	14.2	4.57	7,350	51	..	28	10	1			
4/21/47	.....	....	....	.....	..	..	..	..	..	Same		
4/23/49	.....	....	....	.....	..	..	..	..	..	No change		

* W. C., a girl born March 1, 1924, was 14 years of age at the onset of illness. She had the same symptoms as her sister and mother, with onset about a week later. She showed much weakness and sweating with loss of weight, substernal and indefinite abdominal pain and a hard, dry cough, nonproductive and with no blood. Much prostration was felt, with few signs apparent on physical examination. In the opinion of the family physician she had pulmonary tuberculosis.

† Wintrobe method.

TABLE 3.—*Correlation of Sedimentation Rate, Blood Count, Roentgenographic Changes and Results on Culture with Progress of Treatment in Patient A. C.**

Date	Sed. Rate, Mm./Hr.† Hematocrit, Cu. Mm.	Hemoglobin, Gm. per 100 Cc.	Red Blood Cells, Millions	White Blood Cells	Polymorphonuclear Neutrophils %	Polymorphonuclear Eosinophils %	Lymphocytes Small %	Lymphocytes Large %	Monocytes %	Roentgenographic Appearance	Sputum Culture	Culture of Bronchoscopic Smear
Admitted to hospital inpatient department: Syrup of "calcidrins," 1 dr. 4 times a day; KI, 15 gr. 4 times a day												
4/ 9/38	36/41	10.3	3.94	9,900	65	2	24	8	1	Feathery densities apexes to bases		
5/21/38	38/40	10.9	4.07	10,450	71	2	20	5	2	Large hilar markings	Monilia yeast cells	
6/ 7/38	10/25	....	....	11,850	67	3	27	2	1	Same	Monilia	
6/22/38	34/34	12.4	4.28	14,800	67	3	24	6	1			
Discharged to outpatient department: KI, 20 gr. 4 times a day												
7/ 9/38	.....	10.1	3.92	9,400	73	1	16	5	5	More condensed; less fluffy		
7/30/38	34/39	11.2	4.01	11,700	60	..	29	7	4	.....	Oidium matalense	
8/27/38	34/37	10.7	3.91	12,000	67	1	26	7	5	Same		
10/15/38	38/42	12.0	4.16	9,950	68	2	22	..	3	More condensed		
Moved out of area March 25, 1939												
Readmitted to hospital inpatient department May 10, 1940: KI, 60 to 120 gr. 3 times a day; NaI, 10 Gm. in 100 cc. of water intravenously daily										Dense diffuse fibrosis	Yeast cells	
5/13/40	.....	11.2	4.14	7,650	63	2	30	5	..	Increased fibrosis	Aspergillus	
6/13/40	36/45	12.3	4.50	10,400	72	1	21	3	3	Same	Yeast cells	
7/10/40	29/45	13.1	4.50	13,150	65	..	28	7	1	Same		
8/15/40	.....	13.3	4.65	9,450	65	2	27	6	..	Same		
Discharged to outpatient department												
10/15/40	20/43	13.5	4.50	7,200	56	5	27	10	2	Beginning calcification in rt. lung area		
12/10/40	17/46	13.5	4.49	9,500	67	3	22	5	3	Increased hilar markings		
12/19/40	.....	....	....	.....	..	..	..	..	..	.....	Monilia pinoyi	
Readmitted to hospital inpatient department Jan. 3, 1941: KI, 60 gr. 3 times a day daily; oxyphenarsine hydrochloride, 25 mg. in 300 cc. of 10% dextrose solution intravenously daily for 7 days												Mucor
1/ 4/41	18/45	14.0	4.84	8,700	71	2	18	3	6	Same		Monilia pinoyi
1/13/41	20/44	12.7	4.55	9,450	73	4	20	2	1	Same		
1/22/41	.....	12.7	4.71	10,800	58	7	29	4	1			
2/ 8/41	17/43	12.3	4.36	11,100	70	3	22	5	..	More calcification		
Discharged to outpatient department Feb. 18, 1941												
3/ 7/41	25/42	11.7	....	.....	..	..	..	..	..			
4/30/41	21/44	12.9	4.48	8,000	50	1	39	2	8	Same		
Readmitted to hospital inpatient department May 1, 1941: Ethyl iodide, 4 cc. inhalation 5 times a week for 4 weeks												
5/ 1/41	21/44	12.5	4.36	11,750	63	3	28	2	4			
6/ 6/41	13/45	12.7	4.56	9,150	48	3	37	4	8	Same		
Discharged to outpatient department: Autogenous vaccine—Aspergillus (W. C.) Monilia (P. C.) in increasing dosage weekly for 50 weeks												
6/20/41	13/41	11.2	4.30	8,000	55	22	41	2	..			
7/28/41	16/44	14.0	4.50	9,000	46	1	45	6	2			
8/25/41	8/46	14.2	4.63	7,000	41	2	54	3	..	Same		
10/ 4/41	12/44	13.5	4.61	7,350	42	7	49	2	..			
Aspergillus (W. C.) and Monilia (P. C.) in increasing dosage weekly for 50 weeks												
11/10/41	6/47	14.0	5.01	10,150	84	..	14	2	..	More dense calcification	Yeast cells	
12/ 6/41	13/43	12.7	4.37	8,650	57	5	34	3	1	Same		
2/13/42	11/46	14.0	4.51	10,800	73	1	25	1	..	Same		
6/ 6/42	14/45	14.6	4.79	10,000	56	3	34	3	4	Same		
9/12/42	10/45	14.9	4.14	5,800	46	1	32	11	10	More dense scattered calcified nodules		
10/ 3/42	10/43	14.0	4.58	6,400	53	..	39	1	7			
3/26/44	9/42	14.5	4.67	8,900	55	1	36	8	..			

* A. C., a boy born May 22, 1927, was 11 years of age at the onset of illness. He showed the same symptoms as his sisters and mother, but they were less severe. The onset was less acute, with weakness, sweating and nonproductive cough causing substernal pain. He returned to school three weeks after onset without exacerbation but with continued weakness, sweating, hard, frequent coughing and loss of weight. His recovery was protracted.

† Wintrobe method.

TABLE 4.—*Correlation of Sedimentation Rate, Blood Count, Roentgenographic Changes and Results on Culture with Progress of Treatment in Patient P. C.**

Date	Sed. Rate, Mm./Hr.† Hemato-crit, Cu. Mm.	Hemo-globin, Gm. per 100 Cc.	Red Blood Cells, Millions	White Blood Cells	Polymorpho-nuclear: Neutro-phils, %	Polymorpho-nuclear: Eosin-ophils, %	Lymphocytes: Small, %	Lymphocytes: Large, %	Mono-cytes, %	Roentgeno-graphic Appearance	Sputum Culture	Culture of Broncho-scopic Smear
Admitted to hospital outpatient department; syrup of "calcidrine," 1 dr. 4 times a day; KI, 15 gr. 4 times a day												
4/ 9/38	31/42	10.3	4.06	9,000	69	..	23	7	1	Feathery densities from apexes to bases		
5/28/38	19/47	12.2	4.36	6,450	73	2	24	1	..			
Continued in outpatient department; KI, 20 gr. 4 times a day												
7/ 9/38	13/41	10.3	3.74	4,650	84	2	37	5	2	Same		
7/30/38	13/41	11.6	3.90	5,750	88	2	30	6	4	.....	Oidium matalense	
8/27/38	12/40	11.0	3.76	6,300	43	3	51	3	..	More condensed		
10/15/38	18/42	10.8	4.04	5,200	50	4	42	2	..	Same		
Moved out of area March 25, 1939										More discrete dense nodules		
Admitted to hospital inpatient department May 10, 1940; KI, 60 to 120 gr. 3 times a day; NaI, 10 Gm. in 100 cc. of water intravenously daily												
5/13/40	.....	11.2	4.45	5,300	47	4	43	6	..	Same		
6/13/40	10/40	11.7	4.33	6,100	68	3	22	2	..	Same	Yeast cells	
7/16/40	.....	11.0	4.11	9,500	66	7	25	3	..	More condensed	Yeast cells	
8/14/40	.....	11.9	4.11	7,650	66	2	24	5	3	Same		
Discharged to outpatient department												
10/15/40	15/41	12.3	4.19	7,300	54	5	41	..	..	Same		
12/10/40	12/40	11.9	4.06	6,300	61	2	26	8	3	Same	Monilia pinoyi	
12/19/40	.....	....	....	.....	..	..	..	..	..		Monilia pinoyi	
Readmitted to hospital inpatient department Jan. 3, 1941: KI, 60 gr. 3 times a day daily; oxyphenarsine hydrochloride, 25 mg. in 200 cc. of 10% dextrose solution intravenously daily for 7 days											Mucor Monilia pinoyi	
1/ 4/41	17/41	....	....	.....	..	..						
1/14/41	19/39	11.8	4.53	8,300	66	2	23	5	4	Same		
1/22/41	12/38	9.8	3.75	7,750	78	1	12	4	5			
2/ 8/41	18/38	10.6	4.15	7,500	70	1	28	1	..	Same		
Discharged to outpatient department												
3/10/41	17/38	11.0	4.11	9,650	81	..	18	..	1	Same		
Readmitted to hospital inpatient department: Ethyl iodide, 4 cc. inhalation 5 times a week for 4 weeks												
4/17/41	21/40	12.1	4.42	7,500	88	2	43	2	..	Same		
5/28/41	17/41	11.2	4.30	6,950	53	1	43	..	3	Condensing miliary fibrosis; beginning calcification		
6/ 6/41	13/38	11.4	4.17	7,500	63	1	29	3	4			
6/14/41	Transverse myelitis (spinal fluid showed Monilia on culture)											
10/ 2/41	12/40	12.3	4.70	7,050	60	..	33	5	..	Same		
11/26/41	27/42	11.4	4.50	7,150	61	2	22	8	6	Same		
2/25/42	13/44	14.0	4.98	4,120	50	2	35	10	3	More calcified nodules		
6/11/42	16/39	11.2	4.37	7,200	62	..	37	1	..	More calcification		
8/24/42	8/39	13.1	4.52	8,250	59	..	28	9	4	Same		
1/25/43	9/40	11.9	4.38	6,000	63	1	34	1	1			
8/10/43	10/40	12.5	4.61	8,100	68	..	24	2	7	Same		
Transferred to orthopedic hospital Sept. 15 1943										Extensive miliary calcification		
4/26/47	.....	....	....	.....	..	..	..	..	..	Discrete miliary calcification		
8/23/49	.....	....	....	.....	..	..	..	..	..	Increased calcification at base		

* P. C., a girl born March 27, 1926, was 12 years of age at the onset of illness. She displayed the same symptoms as others in family but they were less acute and less severe. She was not confined to bed and remained at home to help the mother. She was followed in the outpatient department. Roentgenographic findings were similar to those of her sisters. She was treated with iodides and iron from April 9, 1938 to March 29, 1939. Her first admission to the hospital was May 10, 1940. Her symptoms continued to be mild and loss of weight slight. Transverse myelitis developed.

† Wintrobe method.

TABLE 5.—*Intradermal Reactions Showing Degree and Type of Sensitivity to Various Tuberculin and Fungus Preparations and Antibody Response to Autogenous Fungi*

J. C., 15 Yr. of Age

Substance	Amount Given	Date and Reaction* 3/25/38 Im.	3/25/38 Del.	5/4/38 Im.	5/4/38 Del.	6/8/38 Im.	6/8/38 Del.	5/11/40 Im.	5/11/40 Del.	4/1/48 Im.	4/1/48 Del.
Tuberculin (old tuberculin)	0.001 to 1 mg.	..	0	..	..	..	..	..	0	..	0
Tuberculin (purified protein derivative)	0.001 to 1 mg.	..	..	..	0	..	..	..	..	..	..
Tuberculin, avian	0.001 to 1 mg.	..	..	..	..	..	0	..	..	..	..
Brucellin and "brucellergen"†	0.1 cc.	..	..	0	0	..	..	..	..	..	..
Autogenous Monilia (J. C.)	0.1 cc.	..	..	..	..	0	2	..	..	..	..

Substance	Amount Given, Cc.	Date and Reaction* 12/19/40 Im.	12/19/40 Del.	2/11/41 Im.	2/11/41 Del.	6/12/42 Im.	6/12/42 Del.	9/4/42 Im.	9/4/42 Del.	4/1/48 Im.	4/1/48 Del.
Autogenous Monilia (P. C.)	0.1	..	..	4	0	3	0	4	3	..	..
Autogenous Aspergillus (W. C.)	0.1	..	..	4	0	4	0	4	0	..	..
Coccidioidin (stock)	0.1	..	..	0	0	0	0	0	0	..	..
"Oidiomycin"† (stock)	0.1	0	3	3	4	2	4	4	4	..	..
Trichophytin (stock)	0.1	0	0	3	0	2	0	4	3	..	..
Aspergillus (stock)	0.1	4	0	3	0	3	0	4	4	..	..
Penicillium (stock)	0.1	4	0	4	3	4	4	4	3	..	..
Alternaria (stock)	0.1	4	4	4	4	4	4	4	4	..	..
Staph. aureus (stock)	0.1	3	0	0	0	0	0	0	0	..	..
Hemolytic streptococcus (stock)	0.1	0	0	0	0	0	0	0	0	..	..
Neisseria catarrhalis (stock)	0.1	0	0	0	0	0	0	0	0	..	..
Histoplasmin; 1:100 dilution	0.1	..	..	..	..	..	..	..	..	..	4

Complement fixation titer for Monilia (P. C.)‡ 44430
Complement fixation titer for Aspergillus (W. C.)‡ 10000
Agglutination titer for Monilia (P. C.)‡ ..... 1 to 160
Agglutination titer for Aspergillus (W. C.)‡ ..... Unsatisfactory

W. C., 14 Yr. of Age

Substance	Amount Given	Date and Reaction* 3/25/38 Im.	3/25/38 Del.	5/4/38 Im.	5/4/38 Del.	6/8/38 Im.	6/8/38 Del.	5/20/40 Im.	5/20/40 Del.	4/1/48 Im.	4/1/48 Del.
Tuberculin (old tuberculin)	0.001 to 1 mg.	..	0	..	..	..	..	..	0	..	0
Tuberculin (purified protein derivative)	0.001 to 1 mg.	..	..	..	0	..	..	..	..	..	..
Tuberculin, avian	0.001 to 1 mg.	..	..	..	..	..	0	..	..	..	..
Brucellin and "brucellergen"†	0.1 cc.	..	..	0	0	..	..	..	..	..	..
Autogenous Monilia (J. C.)	0.1 cc.	..	..	..	..	0	2	..	..	..	..

Substance	Amount Given, Cc.	Date and Reaction* 12/19/40 Im.	12/19/40 Del.	2/10/41 Im.	2/10/41 Del.	6/12/42 Im.	6/12/42 Del.	9/4/42 Im.	9/4/42 Del.	4/1/48 Im.	4/1/48 Del.
Autogenous Monilia (P. C.)	0.1	..	..	4	0	4	0	4	3	..	..
Autogenous Aspergillus (W. C.)	0.1	..	..	4	0	4	0	0	0	..	..
Coccidioidin (stock)	0.1	..	..	0	0	0	0	0	0	..	..
"Oidiomycin"† (stock)	0.1	0	4	0	3	0	0	0	3	..	..
Trichophytin (stock)	0.1	0	0	0	0	3	0	0	0	..	..
Aspergillus (stock)	0.1	4	0	3	0	4	0	3	3	..	..
Penicillium (stock)	0.1	4	0	3	0	4	0	3	3	..	..
Alternaria (stock)	0.1	4	4	4	4	4	0	4	4	..	..
Staph. aureus (stock)	0.1	3	0	0	0	0	0	0	0	..	..
Hemolytic streptococcus (stock)	0.1	0	0	0	0	0	0	0	0	..	..
Neisseria catarrhalis (stock)	0.1	0	0	0	0	0	0	0	0	..	..
Histoplasmin; 1:100 dilution	0.1	..	..	..	..	..	..	..	..	..	4

Complement fixation titer for Monilia (P. C.)‡ 44430
Complement fixation titer for Aspergillus (W. C.)‡ 23000
Agglutination titer for Monilia (P. C.)‡ ..... 1 to 160
Agglutination titer for Aspergillus (W. C.)‡ ..... Unsatisfactory

TABLE 5.—*Intradermal Reactions Showing Degree and Type of Sensitivity to Various Tuberculin and Fungus Preparations and Antibody Response to Autogenous Fungi*—(Continued)

A. C., 11 Yr. of Age

Substance	Amount Given	Date and Reaction* 4/18/38 Im.	4/18/38 Del.	5/4/38 Im.	5/4/38 Del.	6/8/38 Im.	6/8/38 Del.	5/20/40 Im.	5/20/40 Del.	9/4/42 Im.	9/4/42 Del.
Tuberculin (old tuberculin)	0.001 to 1 mg.	..	0	..	..	..	..	..	0	..	0
Tuberculin (purified protein derivative)	0.001 to 1 mg.	..	..	..	0	..	..	..	..	..	..
Tuberculin, avian	0.001 to 1 mg.	..	..	..	..	..	0	..	..	..	..
Brucellin and "brucellergen"†	0.1 cc.	..	..	0	0	..	..	..	..	..	..
Autogenous Monilia (J. C.)	0.1 cc.	..	..	..	..	0	2	..	..	..	..

Substance	Amount Given, Cc.	Date and Reaction* 12/19/40 Im.	12/19/40 Del.	2/10/41 Im.	2/10/41 Del.	6/12/42 Im.	6/12/42 Del.	9/4/42 Im.	9/4/42 Del.	4/9/38 Im.	4/9/38 Del.
Autogenous Monilia (P. C.)	0.1	..	..	4	0	4	0	4	3	..	..
Autogenous Aspergillus (W. C.)	0.1	..	..	4	0	4	0	4	0	..	..
Coccidioidin (stock)	0.1	..	..	0	0	0	0	0	0	..	..
"Oidiomycin"† (stock)	0.1	0	3	4	4	4	4	4	4	..	..
Trichophytin (stock)	0.1	0	0	0	0	4	0	0	0	..	..
Aspergillus (stock)	0.1	4	0	4	0	4	0	4	0	..	..
Penicillium (stock)	0.1	4	0	4	0	4	0	4	0	..	..
Alternaria (stock)	0.1	4	4	4	4	4	0	4	4	..	..
Staph. aureus (stock)	0.1	0	0	0	0	0	0	0	0	..	..
Hemolytic streptococcus (stock)	0.1	0	0	0	0	0	0	0	0	..	..
Neisseria catarrhalis (stock)	0.1	0	0	0	0	0	0	0	0	..	..
Histoplasmin, 1:100 dilution	0.1	..	..	..	..	..	..	..	..	..	..

Complement fixation titer for Monilia (P. C.)‡ 44410
Complement fixation titer for Aspergillus (W. C.)‡ 10000
Agglutination titer for Monilia (P. C.)‡ ..... 1 to 160
Agglutination titer for Aspergillus (W. C.)‡ ..... Unsatisfactory

P. C., 12 Yr. of Age

Substance	Amount Given	Date and Reaction* 4/9/38 Im.	4/9/38 Del.	6/30/38 Im.	6/30/38 Del.	7/30/38 Im.	7/30/38 Del.	6/3/40 Im.	6/3/40 Del.	4/1/48 Im.	4/1/48 Del.
Tuberculin (old tuberculin)	0.001 to 1 mg.	..	0	..	..	..	..	..	0	..	0
Tuberculin (purified protein derivative)	0.001 to 1 mg.	..	..	..	0	..	..	..	..	..	..
Tuberculin, avian	0.001 to 1 mg.	..	..	..	..	..	0	..	..	..	..
Brucellin and "brucellergen"†	0.1 cc.	..	..	..	..	..	..	..	..	..	..
Autogenous Monilia (J. C.)	0.1 cc.	..	..	..	..	0	2	..	..	..	..

Substance	Amount Given, Cc.	Date and Reaction* 12/19/40 Im.	12/19/40 Del.	2/10/41 Im.	2/10/41 Del.	6/12/42 Im.	6/12/42 Del.	9/4/42 Im.	9/4/42 Del.	4/1/48 Im.	4/1/48 Del.
Autogenous Monilia (P. C.)	0.1	..	..	4	0	4	0	4	0	..	..
Autogenous Aspergillus (W. C.)	0.1	..	..	4	0	4	0	4	0	..	..
Coccidioidin (stock)	0.1	..	..	0	0	0	0	0	0	..	..
"Oidiomycin"† (stock)	0.1	0	3	3	4	3	4	4	4	..	..
Trichophytin (stock)	0.1	0	0	0	0	0	0	0	2	..	..
Aspergillus (stock)	0.1	4	0	4	0	3	0	0	3	..	..
Penicillium (stock)	0.1	4	0	4	0	4	0	4	3	..	..
Alternaria (stock)	0.1	4	4	4	4	4	4	4	4	..	..
Staph. aureus (stock)	0.1	3	0	0	0	0	0	0	0	..	..
Hemolytic streptococcus (stock)	0.1	0	0	0	0	0	0	0	0	..	..
Neisseria catarrhalis (stock)	0.1	0	0	0	0	0	0	0	0	..	..
Histoplasmin, 1:100 dilution	0.1	..	..	..	..	..	..	..	..	..	4

Complement fixation titer for Monilia (P. C.)‡ 45000
Complement fixation titer for Aspergillus (W. C.)‡ 10000
Agglutination titer for Monilia (P. C.)‡ ..... 1 to 160
Agglutination titer for Aspergillus (W. C.)‡ ..... Unsatisfactory

* Im. indicates immediate reaction and Del., delayed reaction.

† "Brucellergen" is a suspensoid of nucleoprotein from Brucella cells, and "oidiomycin" is a broth culture product of Monilia albicans.

‡ Repeat tests one month after date indicated gave identical results.

and small town schools in southeastern Michigan, and, subsequently, they were observed in the hospital clinic, with attention toward correction of defects found. J. C., W. C., A. C. and P. C. were the younger children of a thrifty Polish family living in meager circumstances in an old frame house on a small farm in a low, flat country area. They were cheerful youngsters with a history of good general health, but all were more than 10 per cent below the estimated weight for height and age. All had carious teeth and large cryptic tonsils, with which were associated enlarged cervical lymph glands and midcardiac systolic murmurs considered to be functional. The carious teeth were extracted and tonsils and adenoids were removed during the year preceding the onset of the acute illness. Routine tuberculin tests gave negative reactions. Schick reactions were positive, and the children were immunized against diphtheria. When they were seen for fall school-health appraisal four months before the onset of their acute illness, general nutrition was improved in all. The somewhat nondescript heart murmurs were unchanged. There were no general complaints. Pathologic diagnoses of sections of tonsils removed from all 4 children were reported as "chronic tonsillitis, nontuberculous."

The 3 girls, J. C., W. C. and P. C., were 15, 14 and 12 years old, respectively, the boy, A. C., was 11 years old, and their mother was 55 years old at the onset of their illnesses. After being in good health throughout the winter, they became acutely ill with "flu type" respiratory symptoms during January and February 1938—the mother first, J. C. about three weeks later, W. C. about four weeks later and A. C. and P. C., but less severely, at about this same time. The onset, in varying degrees of severity, was characterized by fever, chills, general malaise, weakness, sweating and hard, dry, distressing cough. They were cared for by the local physician for "la grippe," and all showed transient recovery after one to two weeks of more or less severe, acute symptoms.

A brother, 16 years old, and the father, also living in the home at this time, were not ill. The brother, however, during the following winter had an acute fulminating illness diagnosed as atypical pneumonia and died in a relapse about two weeks after the onset of his illness. Only the clinical diagnosis of pneumonia was made and an autopsy was not performed. Roentgenologic examination of the chest of this brother on April 9, 1938, during the subacute phase of the illnesses of the other children and the mother, showed a few old calcified glands around the hilar area; otherwise the lungs were clear. A test (Mantoux) with 0.1 mg. of old tuberculin gave a negative reaction. Roentgenologic examination of the father also showed a normal appearance at this time.

The progress of the illnesses of the 4 children is shown by the pertinent data regarding medication, sedimentation rate, blood count, roentgenologic interpretation, and results of sputum culture and culture of material obtained by bronchoscope presented in tables 1, 2, 3 and 4.

The only data for the mother consisted of three roentgenograms of the chest obtained June 11, 1938, Sept. 3, 1938 and March 25, 1939. These showed hematogenous type of infiltration scattered throughout both pulmonary fields from apexes to bases. The individual lesions were fairly well circumscribed, with soft, feathery borders, but nodular in appearance. The lesions were similar in all respects to those seen roentgenologically in the 4 children, but denser in distribution. The last roentgenogram showed the lesions more confluent anteriorly, with the apexes fairly well mottled with parenchymatous infiltration. The lesions on roentgenograms appeared more serious than those of the children. The mother was killed in an accident about one year later and autopsy or other examination was impossible. The

family had moved to another locality about 100 miles (161 Km.) distant but also in a low, flat, southern Michigan area. However, it was learned that the mother had continued to have mild malaise with substernal pain and a dry cough which was nonproductive but had remained active at her farm work and the care of her household.

Of the children, A. C. and P. C. had relatively mild initial acute symptoms and helped with the housework and cared for the others who were ill. P. C. insisted on remaining at home to help her mother with the housework and refused admission

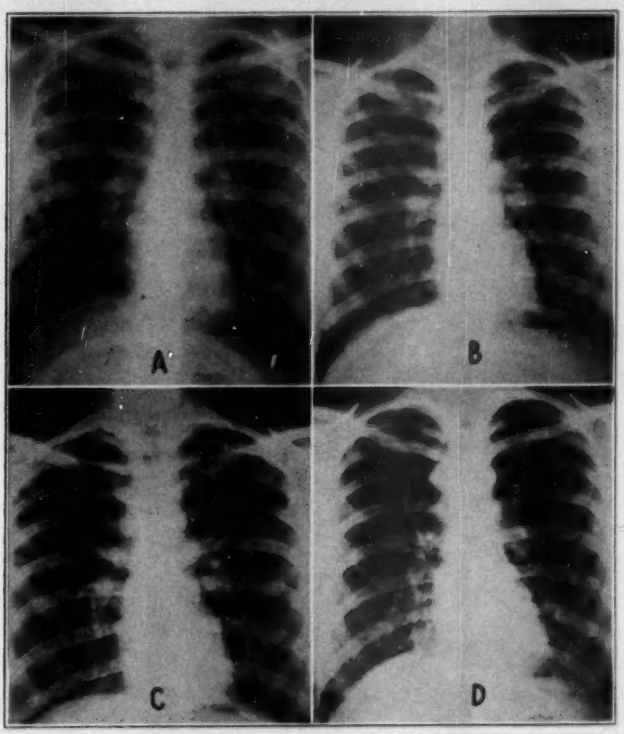

Fig. 1.—Roentgenograms of patient J. C.: *A* (April 6, 1938), soft, fluffy, feathery densities of parenchymal infiltration from apexes to bases; *B* (July 9, 1938), more dense and discrete feathery parenchymal infiltration; *C* (March 25, 1939), less fluffy, more discrete and condensed densities from apexes to bases, and *D* (Aug. 15, 1940), increasing fibrosis with discrete condensation of nodules.

to the hospital until May 10, 1940. She was treated through the outpatient department while she was in the area; she had relatively mild symptoms with some substernal pain and general malaise from time to time, but she proved to have the most protracted course, with development of transverse myelitis. A

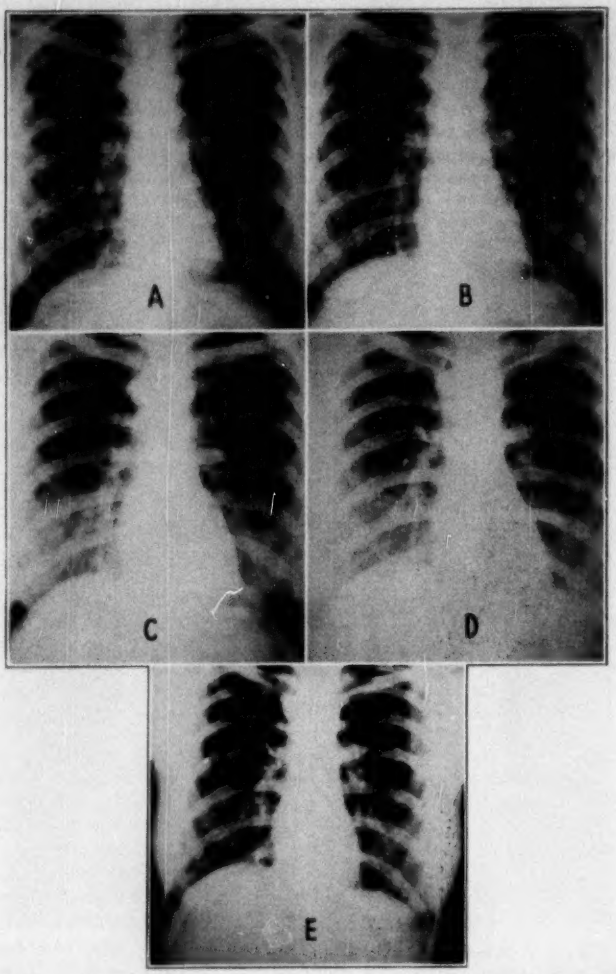

Fig. 2.—Roentgenograms of patient J. C.: *A* (April 30, 1941), fibrosis with definite beginning calcification of nodules and hilar areas about the same as in previous roentgenograms except for increasing fibrosis; *B* (June 6, 1942), increasing calcification of fibrotic nodules and progressive condensation of areas with clearing of apexes; *C* (Feb. 26, 1944), increasing calcification of the nodules and decreasing surrounding bronchovascular markings; *D* (April 21, 1947), some possible increase in the condensation of discrete calcium nodules and more clearing of the parenchymal areas between the nodules, and *E* (April 23, 1949), appearance unchanged, with discrete calcium nodules and clear parenchymal areas between the nodules.

culture of spinal fluid, obtained June 14, 1941, showed a growth of Monilia pinoyi. Her transverse myelitis, affecting the lower limbs, in 1949 had shown no improvement, although the bronchomoniliasis had been completely arrested. J. C. and W. C. both had relapses a few weeks after recovery from the acute phase of their illness; substernal pain and a dry, distressing cough developed with raising of scant, blood-streaked sputum on one or two occasions. The physician who cared for them in the country had heard no significant pulmonary sounds at any time and

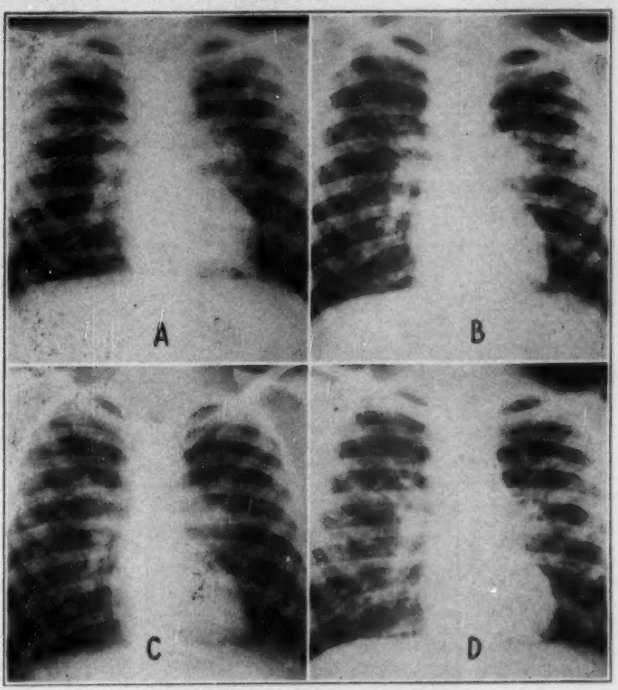

Fig. 3.—Roentgenograms of patient A. C.: *A* (April 9, 1938), soft, fluffy, feathery densities in parenchyma from apexes to bases and large glandular shadows in hilar areas; *B* (July 9, 1938), some condensation of fluffy nodules throughout pulmonary fields with increase in hilar shadows; *C* (Oct. 8, 1938), little change in condensing feathery nodules and dense hilar shadows, and *D* (March 25, 1939), more condensation of nodular areas with beginning fibrosis and no definite evidence of calcification.

referred them into the hospital as having possible pulmonary tuberculosis. Both had a protracted recovery. All these persons have been especially free from respiratory infections since recovering from their pulmonary illnesses.

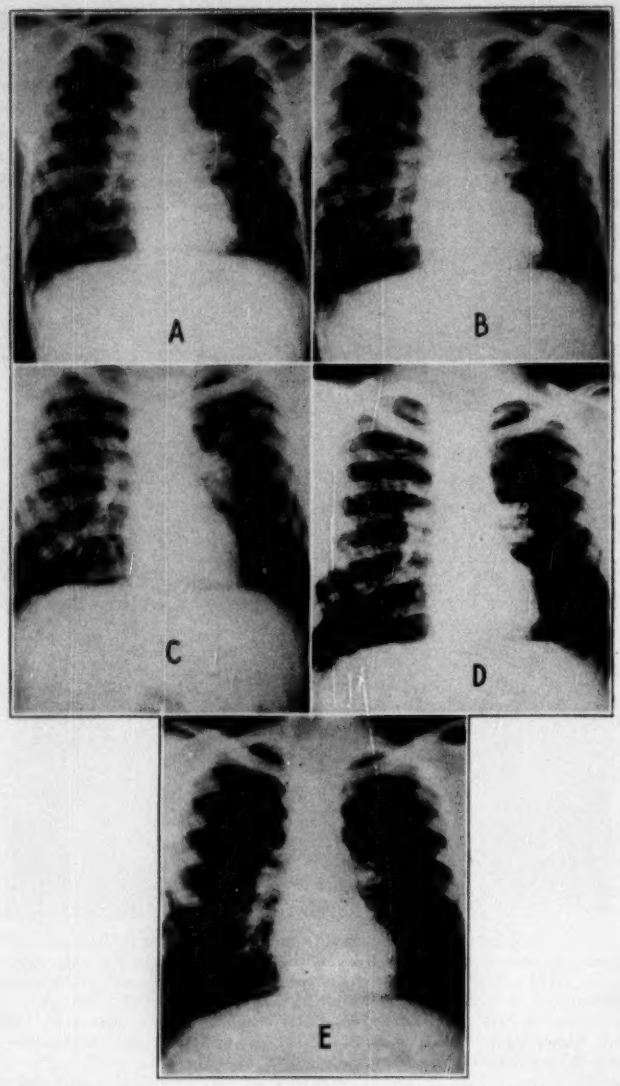

Fig. 4.—Roentgenograms of patient A. C.: *A* (May 11, 1940), increasing condensation of fibrotic nodules throughout both lungs with no definite evidence of calcification; *B* (Oct. 15, 1940), first evidence of calcification in right lung with increase in hilar density; *C* (Feb. 8, 1941), more definite calcification, with some condensation of hilar areas; *D* (Nov. 18, 1941), definite scattered calcification in right lung and in left hilar area, and *E* (Sept. 4, 1942), numerous calcifying nodules in both lungs, with dense calcification of hilar areas.

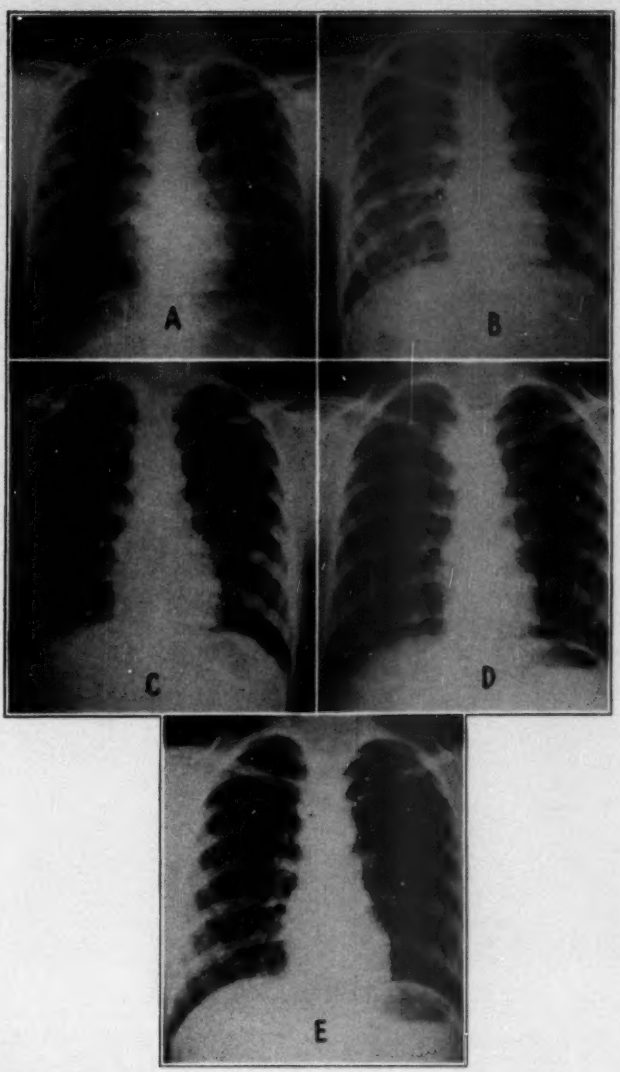

Fig. 5.—Roentgenograms of patient W. C.: *A* (March 28, 1938), soft nodules with fluffy, indefinite outline from apexes to bases; *B* (July 9, 1938), increase in density of parenchymal nodules, more well defined and less fluffy in appearance; *C* (March 25, 1939), more discrete, smaller nodules with beginning fibrosis; *D* (May 11, 1940), increasing fibrosis of nodules and no definite evidence of calcium deposition, and *E* (Dec. 31, 1940), more pronounced condensation of fibrotic nodules, a few appearing with calcium density.

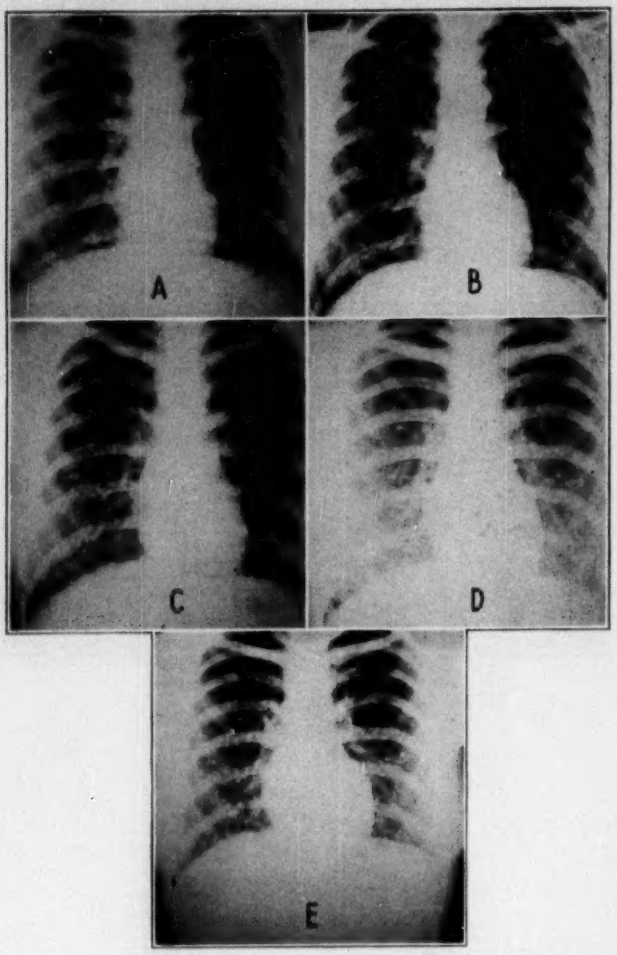

Fig. 6.—Roentgenograms of patient W. C.: *A* (April 29, 1941), more dense, discrete calcification of miliary nodules throughout both lungs; *B* (Sept. 4, 1942), increasing calcification of all nodules and calcifying hilar areas; *C* (Feb. 26, 1944), more densely calcified, shotty nodules of miliary distribution and clearing of internodular parenchyma; *D* (April 21, 1947), discrete condensation of calcium in all nodules with distinct clearing of pulmonary parenchyma between, and *E* (April 23, 1949), appearance unchanged, with dense, discrete calcium nodules and clear parenchyma between.

Physical findings on percussion and auscultation of the chest in all the patients were conspicuous by their persistently normal character, although the roentgenologic pictures showed evidence of extensive parenchymal involvement of the lungs.

The progress of the patients during recovery can be followed best with a discussion of the pertinent data presented in tables 1 through 5 and of the progressive changes in the roentgenographic reproductions shown in figures 1 to 8. The roentgenograms of L. C., the mother, are not reproduced as they showed the

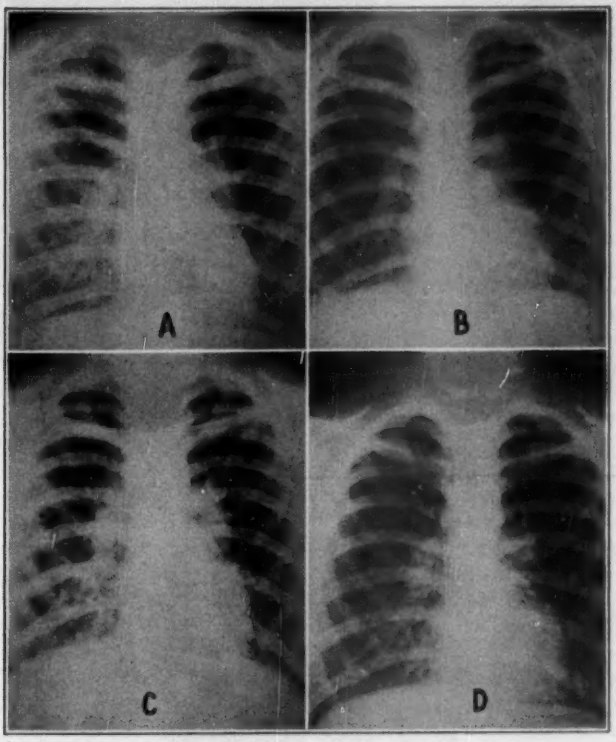

Fig. 7.—Roentgenograms of patient P. C.: *A* (May 28, 1938), fluffy parenchymal nodules in both pulmonary fields from apexes to bases, more densely distributed than in other patients; *B* (Aug. 27, 1938), slightly less fluffiness of borders of nodules; *C* (March 25, 1939), increasing density with more discrete nodulation of parenchymal lesions from apexes to bases, and *D* (July 6, 1940), possible slight clearing of apical parenchyma but little change in nodulation.

characteristic changes found in the other members of the family early in the disease, except that the parenchymal involvement was of greater intensity and the feathery appearance of the densely distributed nodular lesions was of more spectacular character.

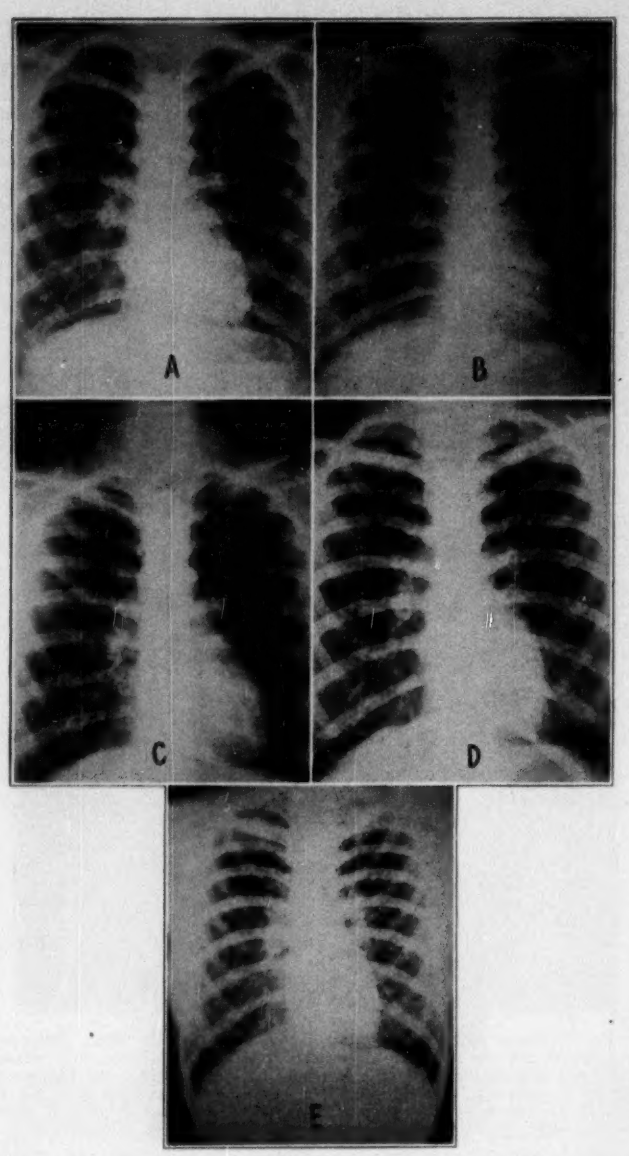

Fig. 8.—Roentgenograms of patient P. C.: *A* (May 20, 1941), condensation of nodules with first evidence of calcium density in some of the nodules; *B* (Sept. 10, 1943), more definite increase in calcium nodules, numerous in both pulmonary fields from apexes to bases; *C* (Feb. 25, 1942), more condensed fibrosis with some increase in number of nodules revealing calcification in both pulmonary fields; *D* (April 26, 1947), dense shotlike calcification of discrete miliary nodules from apexes to bases, with calcification in hilar areas, and *E* (April 23, 1949), definite increase in dense shotlike calcification of discrete miliary nodules, particularly in the bases, with clearing of parenchyma between.

COMMENT

Etiologic Factors.—In published case reports of bronchomoniliasis and aspergillosis, the infection generally is attributed to aspiration of Monilia albicans (Candida albicans) or Monilia pinoyi and Aspergillus niger or Aspergillus fumigatus from some source in nature. Many cases have been explained as due to inhalation of dust from moldy grain during the threshing season or from other sources where mold might have accumulated in abundance. Many investigators stated their belief that the pulmonary tissues must previously have acquired certain characteristics favorable to the growth of these yeast organisms. The cases presented in this report conform with these theories.

During the fall preceding their acute illnesses, all the patients had used old-fashioned flails to pound wheat out of unthreshed stalks on the barn floor for daily chicken feeding. They also had inhaled a great amount of moldy dust during this period while working in the fields during the harvesting of grain and hay. In addition, during the same fall, they had gathered wild grapes and elderberries in the fence rows, the fruit often being covered with a grayish mold. All were undernourished at that time and, although they had no definite symptoms, all had a functional type of systolic murmur heard over the midprecordium; a roentgenogram of the chest of P. C. at the time showed a definite increase in her hilar and perivascular markings. During the same period, the mother had bought a great amount of chicken feathers, which were made into large feather beds without sterilization of any kind. All the family, except the older brother and the father, had been sleeping between these feather beds when they contracted their acute illness.

The house was old and the floors were uncovered. Water was obtained from an open, dug well lined with boards which had decayed and fallen into the water. The water pumped from this well contained many bits of decayed wood splinters which were permitted to settle to the bottom of a pail before the supernatant liquid was dipped out for household use.

Cultures were not obtained from specimens of the grain or hay which was handled by these persons, or of the bushes and vines from which grapes and elderberries were gathered. A culture from water taken out of the well yielded a growth of Aspergillus niger, and specimens from the feather beds yielded cultures of Mucor, Penicillium, Alternaria and four strains of Aspergillus, including Aspergillus niger and Aspergillus fumigatus. Rabbits inoculated with a mixture of heavy suspensions of all the organisms intrapulmonarily showed no evidence of infection after two months. The patients had been exposed to these fungi for some time, and before the onset of acute symptoms their sputums would probably have produced a growth of the organisms. It is reasonable to believe that either their tissues had become sensitized to the protein of the organisms or, as suggested in the literature, the acute episode of

illness was "la grippe," or influenza, which produced changes in the respiratory tract that favored continued growth of these organisms. The patients maintained contact with the various fungi during illness by continued use of the feather beds. The possible importance of the water is questionable, inasmuch as there were no gastrointestinal symptoms.

Symptoms.—The symptomatology presented in the literature is confused by indeterminate factors involving severity of the disease and the phase of the disease at which diagnosis was made and observations recorded. If one is to assume a "conditioning" of the pulmonary tissues to provide an environment favorable for the growth of fungi, the onset of the acute phase of illness in these patients must be considered to be the same as any other "la grippe" or influenza infection. These patients were sick with "flu," as were other members of the community at that time. They had varying degrees of prostration, with fever as high as 103 to 104 F., usually about 102 F., for several days. At the onset there were chills, sweating, general malaise, generalized aching, indefinite pain in the wall of the chest and a tracheal type of cough. Partial recovery from this acute phase was quite prompt after one to two weeks. The temperature fell but the pulse remained fast; the patients felt weak and shaky; there was profuse sweating, and the cough became more persistent and distressing during the period of exacerbation, which lasted from three to four weeks. Sputum was produced which was gruel-like in character and occasionally blood streaked. Pain in the chest was mostly substernal in all the patients. The 2 who had the less pronounced exacerbatory symptoms, P. C. and A. C., produced little or no sputum at any time, had little or no elevation in temperature and denied pain in the chest except for mild substernal discomfort. They did, however, complain of easy fatigability, definite weakness, shakiness on over-exertion and profuse sweating.

Two or three months after the episodes of acute illness, the patients' general feeling of well-being, their lack of subjective symptoms and the complete absence of physical signs on examination of the chest disputed the appearance of the roentgenograms and the laboratory data. The patients moved from the area after being treated for about one year. After a year, in which their treatment was unsupervised, in the winter they again had symptoms similar to those of the exacerbatory period following the acute illness but of reduced severity. The chief complaint was a dry cough with substernal pain and indefinite pains in the abdomen and under the ribs. Careful examination elicited no physical findings. Symptoms and complaints were essentially absent this time, except for the transverse myelitis of P. C. which developed while all the patients were being treated with inhalations of ethyl iodide in 1941 (tables 1 to 4).

P. C. was ambulatory at the time and complained of weakness of her legs; quite rapidly neurologic signs developed, with changes from hyperactive deep reflexes to ultimate spasticity. One culture of spinal fluid yielded Monilia pinoyi, but the organism was lost on subculture in an attempt to grow it for animal inoculation. Results of examination of the spinal fluid otherwise were of no diagnostic value. The patient continued to recover from her bronchopulmonary mycosis, with a course similar to that of her brother and sisters. She did not have treatment with autogenous Monilia (P. C.) and Aspergillus (W. C.) vaccine, as her siblings did, because of the neuromyelitis.

The general health and nutrition of all the patients have been excellent since cessation of treatment in 1942. There has not been a problem of anemia and the patients have had remarkable freedom from illness with common respiratory infections. J. C. worked in a war plant during the war, is married and has a daughter. W. C. served in the Women's Army Corps, is married and has a son. A. C. is serving a second enlistment in the Army, is married and has a son. P. C., although she has spastic paralysis of her lower extremities, finished high school and a commercial course and is employed as a medical secretary. All have been told repeatedly, following industrial or Army roentgenologic examinations at various times, that they have calcified miliary tuberculosis.

Laboratory Data.—All the pertinent laboratory data correlated with treatment for each of the 4 children are presented in tables 1 to 4. The mother, L. C., had no treatment or laboratory studies other than roentgenograms of her chest. For all the children, material from sputums, stomach washings and stools was cultured on numerous occasions for tubercle bacilli. All cultures were negative for the organism. Inoculations of guinea pigs with both concentrated sputums and stomach washings from each child gave negative results for tuberculosis.

A guinea pig, inoculated April 1, 1938 with gastric washings from J. C., when killed June 3 showed no tuberculosis but cultures from cut sections of the spleen showed Aspergillus. Another, given an injection at the same time of bronchial sputum from J. C., when killed June 3 showed no tuberculosis, but the spleen showed Penicillium and the liver, Mucor on culture. A guinea pig, inoculated April 8, 1938 with sputum from W. C., died May 9. Cultures were negative for tuberculosis and sections of organs did not show fungi on smear. The yeast organism most commonly found in the sputums of all patients was Monilia pinoyi. This organism and Mucor were grown from culture of a bronchoscopic smear (Jan. 4, 1941) of silver white, plaquelike lesions on the bronchial mucosa of P. C. and A. C. A culture of Aspergillus niger only was grown from bronchoscopic smears (Jan. 4, 1941) made from the hyperemic mucosa of the main bronchi of W. C. and J. C. Bronchoscopy on J. C. and W. C. (May 23, 1938), a few months after the onset of

acute illness, revealed some hyperemia of the bronchial mucosa and profuse mucopurulent discharge. The material taken for culture was not handled satisfactorily, and no growth was obtained. The Monilia commonly obtained from the sputums and from the bronchoscopic smear of the white plaquelike lesions on the bronchial mucosa of A. C. and P. C. always answered the classification requirements of Castellani for Monilia pinoyi.

The literature contains few hematologic data comparable to those given in tables 1 to 4. All the patients had moderate anemia during the period of exacerbation following acute symptoms early in the disease. Intermittent therapy with iron and liver preparations was necessary until healing was complete. The sedimentation rate appears to be valuable in indicating activity of tissue destruction or arrest and complete healing. Each time a patient had an exacerbation of symptoms the sedimentation rate was highly elevated and became reduced after each period of intensive treatment, remaining normal in all instances after fibrosis of the lesions became advanced and calcification of the fibrotic lesions in the lungs became discrete and condensed. The white blood cell and differential counts were similar to those in tuberculous infection at comparable stages.[53] The white blood cell count was elevated slightly above the upper limit of normal range in the active acute phase of the disease, with an increase in polymorphonuclear percentages and in the ratio of granulocytes to lymphocytes. As healing progressed, the total white count decreased and there was an increase in the ratio of lymphocytes to polymorphonuclear forms.

Table 5 presents the results of serologic tests and skin test reactions to serial increasing doses of various tuberculin materials and to autogenous and stock vaccines of various fungi and of the bacterial organisms common to the upper respiratory tract. The first autogenous vaccine applied (June 8, 1938) was made from a culture of sputum carefully obtained from the lower bronchial tract of J. C. and prepared according to the method of Grossi and Balog [54] for intradermal injection. It was made from a suspension of heat-killed organisms and showed a 2 plus delayed reaction when injected intradermally. Throughout the course of illness the patients all retained a residual nodule at the site of injection which caused a burning and itching sensation periodically over a

53. Hamil, B. M.: Tuberculosis in Infants and in Children: White Blood Cell Counts; Evaluation of the Monocyte-Lymphocyte Ratio by Supravital Staining Method, Am. J. Dis. Child. **41**:1023 (May) 1931. Flinn, J. W., and Flinn, R. S.: Leucocytic Picture of Blood as an Aid in Prognosis and Treatment of Pulmonary Tuberculosis, Am. Rev. Tuberc. **20**:347 (Sept.) 1929. Medlar, E. M.: An Evaluation of the Leucocytic Reaction in Blood as Found in Cases of Tuberculosis, ibid. **20**:312 (Sept.) 1929.

54. Grossi, G., and Balog, P.: Clinical and Experimental Studies on Castellani's Pulmonary Moniliasis, J. Trop. Med. **32**:253 (Sept. 16) 1929.

period of about three years. The autogenous vaccine used for skin testing in 1941 was obtained from cultures of bronchoscopic smears from P. C. (Monilia) and W. C. (Apergillus). Vaccines made from these cultures were later used in a course of desensitization treatment.

From the reactions recorded in table 5, which were read as "immediate" during the first forty-five minutes and "delayed" after twenty-four hours, it would seem that the sensitivities of all the patients to each of the autogenous vaccines were almost identical. The reactions seemed to be less pronounced in 1942 after weekly treatment with increasing doses of both these autogenous vaccines for a period of fifty weeks. The degree of reaction to stock vaccine remained about the same throughout the course of the disease, while the reaction to the bacterial organisms of the upper respiratory tract remained negative, an observation which is taken to indicate presumptively that these patients were not of an allergic diathesis.

Material received from Peterson and Christie [41b] for cooperative study of histoplasmosis and pulmonary calcification in Detroit was used for the tests for sensitivity to Histoplasma. Their criteria for interpretation of the degree of reaction were used in the evaluation of the test reactions. The patients who could be tested at the time (April 1, 1948) showed a 4 plus reaction to intradermal injection of 0.1 cc. of 1 : 100 dilution of histoplasmin. Various investigators have repeatedly stated in the literature that when this test elicits a positive reaction it indicates only the reaction of the individual person to fungi in general.

Opinions vary widely regarding complement fixation and agglutination tests with the fungi. Little significance is given to the results of these tests except in the presence of other significant data. Certainly, the complement fixation reaction to autogenous Monilia from P. C. was uniformly significant in each patient. That with Aspergillus from W. C. appears to be significant only in the patient from whom the culture was obtained. Agglutination with Monilia from P. C. was satisfactory. With Aspergillus from W. C., agglutination was not satisfactory because all control serums also agglutinated the organism. Repeated tests with all the tuberculin materials used gave decidedly negative reactions up to a concentration of 1 mg. per test dose (table 5).

Roentgenologic Interpretation.[55]—The similar roentgenologic findings for all patients on the first examination were described as extensive parenchymatous infiltration throughout both lungs extending from apexes to bases, and a roentgenologic diagnosis of hematogenous tuber-

55. A summary of the progress of the patients' conditions as indicated by roentgenograms was included in a paper presented at the thirty-third annual meeting of the Radiological Society of North America, Boston, Nov. 30 to Dec. 5, 1947. Doub, H. P.: Miliary Calcification of the Lung: Etiologic Aspects, Radiology **51**:480 (Oct.) 1948.

culosis was offered. This diagnosis continued to be offered by the roentgenologists for many months until the clinical search, the results of which had not justified such a diagnosis, produced sufficient evidence to eliminate the possibility of tuberculosis conclusively. This situation is typical of the reports in the literature.

The lesions were at first characteristically fluffy and soft in appearance on the roentgenograms. They were more densely scattered throughout the center portion of both lungs, the apexes being relatively free, in contrast to the greater density in the apexes characteristic of parenchymal tuberculosis. As arrest occurred and healing progressed, the fluffy lesions seemed to condense and to become fibrotic in appearance, with increase in the root markings and later with condensation of calcium in all lesions. Speckling was seen in the middle and lower portions of both lungs, which did not change perceptibly over a period of three or four years. There was never any evidence of fluid. The interlobar pleura was visualized sufficiently at some time in all the patients to suggest some thickening.

Reproduction of the roentgenographic picture serially for each patient at different stages in the progress of the disease is presented (figs. 1 to 8) in an effort to show the similarity in all the children. The change in the soft, fluffy parenchymal lesions in the early stage through the period of condensation of these to a fibrotic appearance and the deposition of calcium in a few, then all, of the nodules as healing progressed, with final condensation of these calcium densities scattered throughout the lungs, is shown. These remained relatively unchanged, indicating a completely healed state of the disease in the lung over the last several years, except in the roentgenograms of P. C. in which there was increased density of calcification even in the last two years.

Treatment.—General supportive measures were employed during the acute stage and exacerbatory phase of the disease. The patients were kept in bed, given liberal, high protein hospital diets and encouraged to take abundant amounts of fluids. Contact isolation precautions were practiced for many months, largely because of the lack of definite knowledge of their disease process. Early in the acute exacerbatory periods, blood transfusions were given to correct the moderate degree of anemia. Thereafter, iron was given orally as either ferric ammonium citrate or ferrous sulfate, with a preparation of liver extract.

The lack of a definite diagnosis early in the course of treatment necessitated cautious management and, until the roentgenologic diagnosis of miliary tuberculosis was disproved, or at least determined to be unlikely, syrup of calcidrine®, a mild cough mixture containing calcium iodide, ephedrine hydrochloride and pentobarbital sodium, was given as indicated in tables 1 to 4, and potassium iodide was given cautiously. For four months after their discharge from the hospital, use of potassium

iodide was continued (80 grains [5.2 Gm.] per day in divided doses) under supervision in the clinic until the family moved from the area in November 1938. Despite some correspondence during the next eighteen months and one roentgenologic examination of the chest after six months, the patients did not take iodides with any regularity, nor did they take iron or supportive treatments for the blood.

A family misfortune returned the patients to the area in the spring of 1940, and all displayed a decided increase in the roentgenologic evidence of pulmonary lesions and again showed a moderate degree of anemia. The white blood cell count was elevated, with leukocytosis, increased sedimentation rate, substernal pain, easy fatigability, general weakness and, in all, evidence of a pronounced exacerbatory phase of the disease. A diagnosis of bronchopulmonary mycosis was sufficiently justified at this time to warrant intensive treatment with iodides. Potassium iodide was given in amounts of as much as 120 grains (7.8 Gm.) three times a day. At the same time, 10 Gm. of sodium iodide in 100 cc. of water was given intravenously daily for a period of one month, May 13 to June 13, 1940 (tables 1 to 4). The administration of potassium iodide by mouth was continued until their discharge to the outpatient department three months later. Symptoms of iodism were not observed in any of the patients during this time. Toward the end of the month of daily intravenous injections of sodium iodide, W. C. showed some palpitation and an electrocardiogram revealed tachycardia similar to that seen in hyperthyroidism. All the patients had some increase in pulse rate during this course of treatment and were kept at rest in bed during the period of intravenous sodium iodide therapy.

They were readmitted to the hospital Jan. 3, 1941 for bronchoscopic examination and another course of intense oral potassium iodide therapy. A growth of Aspergillus niger had been obtained from bronchoscopic smears of the hyperemic mucosa of W. C. (Dec. 10, 1940), and at this time a culture of a similar organism, presenting the characteristics of Aspergillus niger, also was obtained from a smear of the hyperemic bronchial mucosa of J. C. The bronchial mucosa of A. C. and P. C. showed silvery white, raised plaques, and a culture from these plaques yielded a growth of Monilia pinoyi.

Because of uncertainty whether both organisms were operative in the production of disease in all these patients, and because Aspergillus was reported to respond less well to potassium iodide therapy than to therapy with some arsenical, the children were given oxyphenarsine hydrochloride N.N.R., 25 mg. in 300 cc. of 10 per cent dextrose solution, intravenously, daily for seven days (Jan. 14 to Jan. 22, 1941). They were discharged to the outpatient clinic Feb. 18, 1941, and the administration of the same daily dosage of potassium iodide by mouth was

continued for three months. Because the sedimentation rates continued to be moderately elevated, particularly in W. C., with complaints of indefinite, substernal, fleeting pain in the chest, although there was little or no cough, the children were readmitted to the hospital May 1, 1941 for inhalation treatment with ethyl iodide, as recommended by Swartz.[56] They were kept ambulatory during this time except for rest periods before and after inhalation of ethyl iodide.

During the fourth week of this treatment, P. C. had weakness of the legs, hyperactive deep reflexes which progressed in forty-eight hours to a diminution in the reflexes, and within a week all the diagnostic neurologic signs of a lower transverse myelitis. One specimen of spinal fluid at this time yielded a growth of Monilia pinoyi which was lost on subsequent transfer for growth for preparation of vaccine and animal inoculation. Examinations of the spinal fluid on May 29, 1941 showed normal pressure, 1 white blood cell and negative Pandy and Kolmer reactions. Chlorides measured 667 mg., sugar, 58 mg. and protein, 20 mg., per hundred cubic centimeters. The mastic test gave a negative reaction, and the Lange reading was 011000000. Culture showed a growth of diphtheroid bacilli in brain broth in seventeen days. On June 14, pressures were normal, with 1 white blood cell and negative reactions to the Pandy and Kolmer tests. Chlorides were 720 mg., sugar, 65 mg. and protein, 15 mg., per hundred cubic centimeters. The mastic and Lange reactions were negative. Culture yielded a growth of Monilia in Sabouraud's agar medium in four days. This was lost on subculture. On June 28, pressures were normal, with no white blood cells and negative Pandy and Kolmer reactions. Sugar measured 59 mg. and protein, 15 mg. per hundred cubic centimeters, with negative readings on the mastic and Lange tests. Culture showed no growth in five days. The cause of this neurologic development remains unknown. All the patients were receiving the same treatment at the same time. This patient had been treated for two weeks with sulfadiazine, following which she had a trial treatment with ethyl iodide for one week before its use was started for the other 3 patients.

Autogenous vaccine from the cultures of Aspergillus from bronchoscopic smears from W. C. and of Monilia pinoyi from P. C. had been prepared. Because of the high degree of cutaneous sensitivity of all the patients to these autogenous vaccines and to stock vaccines of other fungi, it was considered desirable from the standpoint of additional possible exogenous or endogenous reinfection to attempt a course of desensitization. The treatment dose to be given to the patients was determined by intradermal injections of 0.1 cc. of 1:10,000, 1:1,000 and 1:500 dilutions in sterile water of the extracts supplied by the

56. Swartz, footnotes 50 a, b and d, and 51.

laboratory. All the patients showed slight reaction to the 1 : 500 dilution, and injections were given weekly for fifty weeks, with a gradual increase in the dosage from 0.1 cc. of 1 : 500 dilution to 1 cc. of full strength vaccine. Table 5 portrays the results in the patients, as indicated by skin reaction, of injections of these two autogenous vaccines during this period. Treatment with potassium iodide was not given after May 1, 1941, and the condition of all the patients continued to improve without exacerbation.

Adequate administration of iodide was considered to be the measure of greatest value in accomplishing the arrest of disease in these patients. The administration of autogenous vaccine may have reduced the possibility of reinfection by decreasing the degree of allergy, evidenced by diminished intradermal reactions following the course of treatment with the vaccine.

CONCLUSIONS

The simultaneous primary occurrence of bronchopulmonary mycosis (due to Aspergillus niger and Monilia pinoyi) in 5 members of a family group, and possibly a sixth, is unusual in medical literature. A similar instance has not been reported. The origin of the fungi responsible is conjectural but very likely the organisms were from a common source in nature. It is probable that the mucosa of the respiratory tract became sensitized to these pathogenic fungi during the fall and early winter when grain was being threshed within a small enclosure in an old barn, and dust from harvesting both grain and hay in the fields was inhaled in abundance.

It is reasonable to believe that the pathogenicity of the fungi is dependent on the resistance of the host. The "flu"-like respiratory illness at the onset of symptoms was the primary conditioning factor, whether it caused toxic or mechanical irritation, change in the bronchial secretions from alkaline to acid character or produced enhanced tissue susceptibility. Regardless of the specific method, conditions favorable to the pathogenicity of the fungi were established and the clinical picture of primary bronchopulmonary mycosis resulted. Constant contact with the varied and abundant fungi present in the family feather beds was responsible for periodic exogenous reinfection.

Diagnosis of this condition is commonly confused and is hampered by the reluctance of most clinicians to exclude hematogenous tuberculosis as the likely possibility, owing to the classic array of symptoms and characteristic roentgenograms. Such a situation requires an open-minded search for fungi, as well as for tuberculosis organisms, inasmuch as early accurate diagnosis is essential for effective treatment of either condition. The laboratory carries great responsibility for such cases.

Repeated isolation of pathogenic fungi in smear and on culture of bronchial secretions is generally recognized as presumptive evidence

of the significance of these organisms to the disease process in question. Positive reactions to intradermal injection of various extracts of fungi support this presumptive evidence, for patients with systemic fungous infections develop a strong nonspecific sensitivity to heterologous fungi. The consistent absence of a positive reaction to tuberculin and of tubercle bacilli from bronchial secretions justifies a program of treatment uncomplicated by consideration of the possible presence of tuberculosis.

Successful treatment rests chiefly on administration of adequate amounts of iodides. Potassium iodide can be given safely in massive doses by mouth for long periods without toxic effects. Sodium iodide can be given as 10 per cent solution intravenously daily for long periods simultaneously with potassium iodide. Ethyl iodide can be given effectively by inhalation for short periods, without known toxic or unfavorable effects other than those common to iodides in general. A course of treatment with autogenous vaccine may be beneficial in decreasing the susceptibility to exacerbation or reinfection.

Blood counts and sedimentation rates are helpful in evaluating the progress of the patient and the activity of the disease. Anemia accompanies the periods of active invasion and exacerbations of the disease process. The total white blood cell count is increased during these periods and the ratio of polymorphonuclear leukocytes to lymphocytes is high. As healing progresses, these findings are reversed. These data are similar in tuberculosis, nullifying their value in differential diagnosis.

The changes shown in the roentgenograms of the lungs of the 4 children were remarkably similar, except in degree, at all times throughout the ten years of observation. The literature does not contain similar observations over as long a time. However, comparison with reports of various pulmonary mycotic infections shows all to have so much in common that only mycosis in general may be suspected from roentgenograms. There were no pathognomonic findings dissimilar to those of tuberculosis. Under such conditions, positive diagnosis can be made only by identification of the organism. Since exhaustive bacteriologic study is time consuming and not feasible as a routine procedure in all patients with pulmonary infections, the benefit of successful early treatment depends on alertness to suspicious, but not distinguishing, features that indicate conditions in which careful, thorough investigation may produce a positive diagnosis.

Primary bronchopulmonary mycotic infection with Monilia pinoyi and Aspergillus niger healed completely in these 4 children, leaving scattered, dense, miliary calcium nodules throughout the lungs.

The earliest appearance of calcium in the nodules was about three years after intermittent treatment, and within a few months after

intensive treatment with iodides, oxyphenarsine hydrochloride and vaccine. There were no residual symptoms. The successful results are the outcome of persistence in treatment, which would have been more effective if it could have been more adequate earlier in the disease and given with a courage of conviction consistent with the facts.

SUMMARY

Bronchopulmonary mycosis (due to Monilia pinoyi and Aspergillus niger) developed simultaneously in 4 children and their mother with symptoms characteristic of and diagnosed as "la grippe" or "flu." The incriminated organisms were probably in the respiratory tract from a common source in nature (grain and hay dust and contaminated chicken feathers) and became pathogenic as a result of this conditioning illness. The subsequent course of the disease in the children was protracted because of inadequate early treatment. Massive doses of iodides (potassium iodide orally, sodium iodide intravenously and inhalations of ethyl iodide) were followed by progressive healing. The fluffy parenchymal nodules, characteristic of the roentgenograms in all the patients, healed through fibrosis to scattered, complete, dense miliary calcification. The first appearance of calcium in all the patients was about three years after the onset of acute symptoms. Serial blood counts and sedimentation rates showed characteristic changes similar to those observed in tuberculosis. Repeated tests of skin reaction to intradermal injection of various stock fungi and bacterial vaccines and to autogenous Monilia pinoyi and Aspergillus niger vaccines indicated the extent of allergic response to heterologous fungi but also showed the more specific response to the autogenous organisms. Complement fixation and agglutination reactions are presented.

Presentation of progressive roentgenologic changes over ten years of observation indicates the complete healing of the pulmonary lesions consistent with the present good state of health of all the patients.

Miss Edna Jackson, M.S., bacteriologist in the Department of Laboratories, isolated and classified various yeast organisms cultured from these patients. She also carried out the animal inoculation studies and prepared material for vaccines.

Dr. Frank R. Menagh, physician in charge of the Department of Dermatology and Allergy, interpreted and evaluated skin reactions to the fungous preparations. He also outlined dosage for the intensive therapy with iodide and arsenical drugs.

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TREATMENT OF EDEMA IN DISEASE OF THE KIDNEY

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TREATMENT of the edema which accompanies chronic disease of the kidney in children and management of the child during the edematous phase constitute one of the most trying problems in pediatrics. Before we begin a discussion of the treatment of edema of chronic nephritis and nephrosis in children, some remarks regarding classification of diseases of the kidney in children are in order.

The classification which we now use is essentially that first described by Aldrich [1] in 1930 and further explained by him in 1931.[2] Thus, there are the three larger groups: (1) acute postinfectious (glomerular) nephritis; (2) chronic nonspecific (glomerular) nephritis, and (3) nephrosis. This paper is not concerned with acute nephritis, as the control of edema in that condition seldom presents any difficulty. The existence of nephrosis as a clinical entity is usually not admitted by those internists and pathologists who deal exclusively with adults. It is often considered by them as a phase of chronic nephritis, if its presence is discussed.

In our clinic, we have adhered to the principles of differential diagnosis between nephrosis and chronic nephritis outlined by Aldrich, that is, the absence of hematuria, hypertension and azotemia in nephrosis and their presence in chronic nephritis. Obviously, like all other principles in medicine, this rule cannot be rigidly employed in 100 per cent of patients. We have seen children with occasional red blood cells in the urine on one or two examinations who did not show chronic nephritis with severe damage of the kidney; the same observation applies to children with one or two nonprotein nitrogen readings slightly above 35 mg. per hundred cubic centimeters of blood. However, it has been our experience that when a child with "pure" nephrosis begins to have occasional blood cells in the urine or occasional slight elevation of nonprotein nitrogen, these conditions will become more persistent and the child will have chronic nephritis, with severe renal damage and even-

From the Children's Memorial Hospital, Chicago.

1. Aldrich, C. A.: Clinical Types of Nephritis in Childhood, J. A. M. A. **94**:1637 (May 24) 1930.

2. Aldrich, C. A.: Nephritis in Children: Progress and Differential Diagnosis, Am. J. Dis. Child. **41**:766 (April) 1931.

tual death. We have also observed that if such a change does occur it will usually be within the first few months of illness. Rarely will a child with nephrosis have chronic nephritis after six months of illness. One outstanding exception comes to mind: a Negro girl who was ill two years with a diagnosis of nephrosis before hematuria developed. Her condition progressed to severe damage of the kidney and death.

Heymann and Stortzman [3] also made a distinction between nephrosis and chronic nephritis in children. The former was designated as "lipemic" nephrosis. Lipemia, however, is not a differentiating feature, as it is usually present with the edema of chronic nephritis. These authors also observed that in children with nephrosis chronic glomerulonephritis may develop, and the point is stressed that some weeks of observation may be required before a definite diagnosis can be established. Other children's clinics usually differentiate between the two conditions, although the criteria vary.

During the past twenty-five years most of the various treatments suggested for relief of edema in children with chronic nephritis and nephrosis have been tried in our clinic. These include high protein, high vitamin, low salt diet,[4] thyroid in increasing dosage up to the point of toxicity, artificial fever produced by foreign proteins or nirvanol (phenylethylhydantoin), acacia intravenously, acid-ash diet alone and high alkali intake. The last method was described by Schlutz and Collier [5] in 1937 and recently by Fox and McCune.[6] The use of lyophile and liquid pooled serum has also been reported on.[7] More recently, plasma and albumin have been given, the former in large amounts and the latter to a few children only. We have also observed diuresis following acute infections with high fever. Recently, a boy, 6 years old, who had nephrosis for one year, was hospitalized with an attack of peritonitis. On recovery from the peritonitis, he lost all his edema by diuresis. Within one month, his urine was entirely normal and has

3. Heymann, W., and Stortzman, V.: Lipemic Nephrosis, J. Pediat. **28**:117 (Feb.) 1946.

4. Aldrich, C. A., and Boyle, H. H.: Chronic Nonspecific Nephritis; Clinical Observations on Forty Children with Results of Treatment on Full Diets, J. A. M. A. **100**:1979 (June 24) 1933.

5. (*a*) Schlutz, F. W., and Collier, J. L.: The Treatment of Nephrosis in the Young Child, J. A. M. A. **109**:1959 (Dec. 11) 1937. (*b*) Dr. A. Graeme Mitchell, in the abstract of discussion on the paper by Schlutz and Collier, commented: "I have sometimes felt that a patient who did not respond to acid therapy would sometimes respond later to alkali therapy or that the reverse of this might happen."

6. Fox, C. L., and McCune, D. J.: Electrolyte Changes in Nephrosis, Am. J. M. Sc. (July) 1948.

7. Aldrich, C. A.; Stokes, J., Jr.; Killingsworth, W. P., and McGuinness, A. C.: Concentrated Human Blood Serum as Diuretic in Treatment of Nephrosis; Preliminary Report, J. A. M. A. **111**:129 (July 9) 1938. Aldrich, C. A., and Boyle, H. H.: Concentrated Human Blood Serum as a Diuretic in Nephrosis; Further Observations, ibid. **114**:1062 (March 23) 1940.

remained normal for five months. The beneficial effect of measles has been observed by many workers in this field. A recent report by Blumberg and Cassady [8] agrees with observations in our clinic, but complete, permanent recovery following measles has been rare in our experience. One is inclined to agree with Mitchell's [5b] further comment that the treatment of this condition is discouraging. However, the ultimate prognosis for those children who have lipid nephrosis is good. A recent report from the University of Iowa [9] emphasizes this fact.

REPORT OF CASES

A group of 15 children having severe edematous states associated with pathologic changes of the kidney have been followed at this hospital during the past two years. Our major purpose has been control of edema, as well as making the patient more comfortable, increasing oral protein intake by stimulating appetite and increasing urinary output by threatening the kidney with acidosis while using water as a diuretic.

The presenting symptom in all these children was edema, which was generalized in 12 of them and restricted to the face alone in 3. Cloudy or bloody urine was noted grossly in but 3. The average age at onset was 2½ years, and two thirds of the children were boys. All were white except 2 Negroes and 1 Filippino.

It can be said that infection preexistent to pathologic changes of the kidney was the exception in these children, since only 6 had a history of otitis media or tonsillitis two weeks before edema occurred. One child had a history of ingestion of large doses of calomel (mild mercurous chloride U. S. P.) before onset of edema.

A brief review of laboratory findings is as follows:

1. Blood studies revealed normocytic anemia in 12 children. Blood cholesterol varied from 381 to 1,087 mg. per hundred cubic centimeters, with an average of 500 mg. Total protein averaged 4.2 Gm. per hundred cubic centimeters. The albumin to globulin ratio was reversed in 11 children. The 3 instances of no reversal occurred in those with the severest chronic nephritis, which resulted in early death.

2. Urinalyses showed albuminuria in all the children. Hematuria was absent in all those with clinical nephrosis. Absence of blood was noted early in the urines of 4 of the children whose conditions were diagnosed as chronic nephritis, but hematuria appeared at later stages of the disease.

3. Roentgenograms of the chest showed no abnormalities in size of the heart, and electrocardiograms, when done, were normal. Blood pressure was abnormally elevated in only 2 children.

On the basis of clinical and laboratory findings, the states of the group were divided into two entities. The conditions of 5 children fitted into the picture of nephrosis. Their blood studies showed low nonprotein nitrogen and urea nitrogen levels. Urine examinations showed 4 plus reactions for albumin, but samples were consistently negative for blood by benzidine test and microscopic examination

8. Blumberg, R. W., and Cassady, H. A.: Effects of Measles on the Nephrotic Syndrome, Am. J. Dis. Child. **73**:2 (Feb.) 1947.

9. Block, W. M.; Jackson, R. L.; Stearns, G., and Butsch, M. P.: Lipoid Nephrosis: Clinical and Biochemical Studies of Forty Children, with Ten Necropsies, Pediatrics **1**:733 (June) 1948.

of centrifugated specimens. Ten patients had the picture of chronic nephritis. They had high nonprotein nitrogen and urea nitrogen values. Urines revealed a 4 plus reaction for albumin and were positive for blood. The presence of blood in the urine of over four to six months' duration was the most important finding differentiating chronic nephritis from nephrosis. No difference was observed in blood total proteins, albumin to globulin ratios or reversals of ratios, cholesterol levels, states of anemia or blood pressure.

Thirteen of these children had received extensive courses of treatment with plasma, blood or human albumin intravenously, and most of them had required one, or more, abdominal paracentesis—usually within the first month of onset of edema. Because of the difficulty in finding veins in the edematous children, most veins had been destroyed by cut-down procedures. Prolonged treatment was necessary with few superficial veins intact.

The mainstay in our therapy for edema control was the "acid-ash" regimen, most of which procedures were introduced by Schemm[10] and Newburgh and Mackinnon[11] in 1933. We have found no report of the application of this regimen to children. Schemm's clinical work in management of edema was chiefly with that in the cardiac decompensation, eclampsia and nephritis in adults.

The fundamentals of this routine are:

1. The liberal use of fluids, that is, about 50 cc. per pound (0.5 Kg.) of body weight daily for these children. This averaged 1,500 to 2,000 cc. daily. They were given by mouth if possible. In some instances children would not take such large volumes, and then an intranasal Levin tube was used for periods up to one month, allowing tube feedings. In rare cases, fluids of hypotonic nature were given intravenously (5 per cent dextrose solution in distilled water). The purpose of the high fluid intake was to facilitate the work of the damaged kidney in eliminating the mobilized sodium ion. Water itself is known to be a diuretic, as noted in the works of Sir George Baker[12] in 1772. In addition to this, the increased fluid intake allowed hydration of the tissue cells which had actually suffered loss of fluid to the brine-logged tissue interspaces.

2. The acidification of fluids to help mobilize the sodium ion from the alkaline ash mediums of the tissue interspaces. The sodium ion is trapped with the edema fluids in the alkaline marshlands of these interspaces. As Schemm[10] stated, for each 2 pounds (0.9 Kg.) of edema there are about 10 Gm. of an alkaline mixture of sodium salts (about 5 parts sodium chloride with 1 part sodium bicarbonate, yielding a p_H of 7.4) and 1,000 cc. of water as solvent for the salts. To accomplish this acidification, acid drugs were employed. Ammonium chloride as enteric-coated tablets or as a seasoning agent for sprinkling on food was used. This drug was observed to cause nausea in many children, and, therefore, potassium chloride in glycyrrhiza syrup was employed and found to be tolerated better. Diluted hydrochloric acid U. S. P. was used, five drops in a glass of water three to four times daily. Acid fruit juices, such as cranberry, plum and prune, were given,

10. Schemm, F. R.: A High Fluid Intake in the Management of Edema, Especially Cardiac Edema: I. Details and Basis of Régime, Ann. Int. Med. **17**:952 (Dec.) 1942; II. Clinical Observations and Data, ibid. **21**:937 (Dec.) 1944.

11. Newburgh, L. H., and Mackinnon, F.: The Practice of Dietetics, New York, The Macmillan Company, 1934, pp. 7-20, 86-97, 225-244 and 253-258.

12. Baker, G.: Several Extraordinary Instances of the Cure of Dropsy, M. Tr. Coll. Physicians, London.

since all other juices yield an excess of alkaline ash. An acid-ash, high protein diet was found to be taken well. It was comprised chiefly of meat, chicken, fish, eggs and cereal foods.[13]

3. The restriction of sodium chloride to about 1 to 2 Gm. daily. This was done by eliminating salt in cooking, by using salt-free butter and salt-free bread and a new salt-free powdered milk preparation (lonalac®).[14]

The results of therapy indicate that nephrosis responds better than chronic nephritis. Each of the 5 patients with nephrosis has had clearing of substantial amounts of fluid, and 3 of these have been followed in the clinic as free from edema during the past eighteen months. Each of these children has had recurrences of edema, usually with recurring infections, but edema usually cleared rapidly following control of infection with penicillin or sulfadiazine therapy. Diuretic effect was not seen until eight to twenty days after the "regimen" was started. One boy whose condition had been refractory to large quantities of plasma intravenously had a dramatic diuresis on the eighth day of this regimen—in three days his weight had dropped from 47 to 32½ pounds (21.3 to 14.7 Kg.). In twenty-four hours, 6,000 cc. of urine was produced. More frequently, the children lost their edema over a long period of time.

The phenomenon seen in children with chronic nephritis on this regimen was the shifting of edema fluid from face and extremities to serous cavities—particularly the peritoneal cavity. This was noted by previous observers[15] and was of some advantage. Paracentesis could be done to remove ascitic fluid at intervals, while face and extremities remained less edematous and the child was made more comfortable.

Three of the children with chronic nephritis did not respond to any therapy. The conditions of all the children became refractory to repeated infusion of plasma, and those that received plasma were only temporarily benefited.[7] Mercurial diuretics were tried in 2 children, but no diuresis occurred. Ammonium chloride in a twelfth-molar solution[16] was given subcutaneously to test diuretic effects, but the child was rapidly driven into severe acidosis, with a blood carbon dioxide level of 19 volumes per cent, and no diuresis occurred. According to Schemm,[17] a low blood carbon dioxide level does not necessarily indicate acidification of the tissue interspaces, showing that acidosis alone does not insure diuresis.

Three of the children had measles during this period of observation. Following this disease, all 3 had rapid loss of edema with definite diuresis. In each child, following diuresis, a low level of total blood protein became elevated and reversed albumin to globulin ratios became righted. Unfortunately, 1 of these children died two months later of cause unknown, but he was free of edema at death. The other 2 children have pictures of clinical nephrosis and continue to be free of edema.

Seven of the patients with chronic nephritis died within one year of the onset of the edema. No course of therapy seemed to change the course of this dis-

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13. Schemm.[10] Stevenson, I. P.: Modern Management of Oedema, Arizona Med. **4**:105 (March) 1947.

14. This product was furnished by Mead Johnson & Co., Evansville 21, Ind.

15. Aldrich, C. A.: Clinical Course of Generalized Edema, J. A. M. A. **84**:481 (Feb. 14) 1925.

16. Forbes, G. B., and Erganian, J. A.: Subcutaneous Administration of Ammonium Chloride Solution, Am. J. Dis. Child. **72**:649 (Dec.) 1946.

17. Schemm, F. R.: Personal communication to the authors.

ease. Postmortem examination of 6 of these revealed changes of chronic and subacute nephritis, with destruction of glomeruli, hyaline or scar tissue replacement of glomeruli and degeneration of tubular structures.

COMMENT

It will be observed that we do not offer a cure for edema of nephrosis and chronic nephritis. We have felt from clinical observation of our patients that they get along better with this regimen than with any other we have used. All observers know that spontaneous diuresis can, and often does, occur without any apparent reason. Therefore, it is impossible to use controls. Results must be judged by clinical observation of a fairly large number of children over long periods of time. One soon learns that one or two observations of diuresis following any form of treatment have no significance at all.

SUMMARY

1. A classification of disease of the kidney in children is discussed.

2. A series of 15 children is reported on in whom the acid-ash regimen, liberal fluids and restriction of sodium chloride were employed.

3. It is felt that the control of edema, as well as making the patient more comfortable, justifies the use of this regimen in our clinic.

The Nutrition Department of the Children's Memorial Hospital cooperated in preparation of diets used in this study.

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SIX EXAMPLES OF PRECOCIOUS SEXUAL DEVELOPMENT

II. Studies in Growth and Maturation

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IN A PREVIOUS publication[1] 6 children with precocious sexual development were presented from the point of view of diagnosis, pathogenesis and management. The present paper is concerned with the study of growth and maturation in the same 6 children. The patients may be identified by reference to the photographs and diagnostic legends accompanying the earlier publication. The first section of the present paper contains a short description of technics and standards used in these studies. In the second section, anthropologic measurements, results of skeletal and dental examinations and appraisals of sexual and psychologic maturation are presented in tables, photographs and graphic charts; dental and mental development and socioeconomic background are described in more detail in the text. The two remaining sections are devoted to comment and conclusions.

I. TECHNICS AND STANDARDS

A. Anthropometric Studies.—1. Weight and Height (tables 1 to 3): Determinations were made on the usual children's scale, the child assuming the standard position, the body being completely stripped. The standing heights listed in tables 1 and 2 were taken with the anthropometer. Mean values of the Iowa Growth Charts were used for normal standards.[2] Curves for the patients' weights and heights are graphically shown in figures 1 and 2. The two unbroken curves in the upper left of figure 1 were drawn on the hypothesis that infants would continue to grow in weight at approximately the one-half year rate until they were 3 years old and, immediately thereafter, would follow the normal growth curves of adolescents. In other words, the normal "lag phase" of slow increments of growth between about 1 year and 11 or 13 years of age in girls or boys, respectively, was cut out from the human growth curve. Thus, hypothetic growth curves were obtained that resembled those of most higher vertebrate animals.[3]

From the Department of Pediatrics, University of Chicago School of Medicine.

1. Seckel, H. P. G.; Scott, W. W., and Benditt, E. P.: Six Examples of Precocious Sexual Development: I. Studies in Diagnosis and Pathogenesis, Am. J. Dis. Child. **78**:484 (Oct.) 1949.

2. Jackson, R. L., and Kelly, H. G.: Growth Charts for Use in Pediatric Practice, J. Pediat. **27**:215, 1945.

3. Brody, S. A.: Comparison of Growth Curves of Man and Other Animals, Science **67**:43, 1928; Scient. Monthly **59**:208, 1944.

2. Circumference of Head and Chest (tables 1 to 3): These measurements were taken with the child in the upright position, the circumference of the head on the level of the glabella, the circumference of the chest on that of the xiphisternal juncture and in an intermediate respiratory phase. Mean normal standards were used as compiled by Davison.[4]

3. Other Anthropometric Measurements (tables 1 to 3): Somatometric and cephalometric technics were used as outlined in the literature,[5] especially by Krogman and Snodgrasse.[5h] In 2 children (cases 3 and 4, table 2), Broadbent's cephalometric roentgenographic technic was used,[5i] measuring distances on tracings of roentgenograms of frontal and lateral views and applying a correction scale to eliminate distortions. Indexes were calculated as follows: Anterior trunk height index = anterior trunk height/standing height; trunk breadth index = bicristal breadth/biacromial breadth; cephalic index = biparietal head breadth/head length; facial index = face height/bizygomatic breadth. Mean normal standards for anthropometric dimensions were taken chiefly from a study on Chicago private school children [5c] and the Cleveland material [5g]; occasional norms were supplemented from Krogman's data.[5a] In figure 3, schematic representations of body frames, as first suggested by Bowles [6] and later reproduced by Shuttleworth,[7] are given for an average normal 7 year old girl (A) and for one of the present patients, a girl (case 1) 6 9/12 years of age (B). On the graph, total standing heights are indicated by the top points. Lines connecting various points were as follows: horizontal lines, top to bottom: biparietal head breadth, bizygomatic face breadth, biacromial breadth, xiphisternal breadth of the chest, bicristal, bispinous and bitrochanteric breadths; perpendicular lines, central axis: face height = nasion to chin;

4. Davison, W. C.: The Compleat Pediatrician, ed. 6, Durham, N. C., Duke University Press, 1949.

5. (*a*) Krogman, W. M.: Growth of Man, in Tabulae Biologicae, The Hague, Netherlands, Uitgeverij Dr. W. Junk, 1941, vol. 20. (*b*) Baldwin, B. T.: The Physical Growth of Children from Birth to Maturity, University of Iowa Studies in Child Welfare, Iowa City, University of Iowa Press, 1921, vol. 1, no. 1. (*c*) Gray, H., and Ayres, S. G.: Growth in Private School Children with Averages and Variabilities Based on 3,110 Measurings on Boys, and 1,473 on Girls, from the Age of One to Nineteen Years, Chicago, University of Chicago Press, 1931. (*d*) Shuttleworth, F. K.: Sexual Maturation and the Physical Growth of Girls Age Six to Nineteen, Monograph of the Society for Research in Child Development, 1937, vol. 2, no. 5; (*e*) The Physical and Mental Growth of Girls and Boys Age Six to Nineteen in Relation to Age of Maximum Growth, ibid., 1939, vol. 4, no. 3. (*f*) Vickers, V. S., and Stuart, H. C.: Anthropometry in the Pediatrician's Office, J. Pediat. **22**:155, 1943. (*g*) Simmons, K.: The Brush Foundation Study of Child Growth and Development: II. Physical Growth and Development, Monograph of the Society for Research in Child Development, 1944, vol. 9, no. 1. (*h*) Krogman, W. M., and Snodgrasse, R. M.: A Manual of Anthropometry: I. Somatometry; II. Cephalometry, Chicago, 1947 (unpublished). (*i*) Broadbent, B. H.: The Face of the Normal Child, Angle Orthodontist **7**:183 and 209, 1937.

6. Bowles, G. T.: New Types of Old Americans at Harvard and at Eastern Women's Colleges, Cambridge, Mass., Harvard University Press, 1932.

7. Shuttleworth, F. K.: The Adolescent Period: A Graphic and Pictorial Atlas, Monograph of the Society for Research in Child Development, 1938, vol. 3, no. 3.

anterior trunk height = suprasternal notch to symphysis pubis; perpendicular lines, arm: upper arm = acromion to radial head; forearm = radial head to radial styloid process; hand = radial styloid process to middle finger tip; perpendicular lines, leg: thigh = point estimated at one-third the distance between symphysis pubis and midbicristal breadth to tibiale; lower leg = tibiale to inner malleolus (sphyrion); foot = sphyrion to sole.

4. Skeletal Ossification Centers (table 4): Six major skeletal areas were studied by roentgenogram in each patient, namely, shoulder, elbow, hand, pelvis, knee and foot. Additional routine roentgenograms of chest and skull contributed information on vertebral bodies, ribs, cranial sutures and intracranial calcifications. The most spectacular findings were reproduced in figures 4 to 6. As standards for the assessment of skeletal age, data presented by Hodges and Todd[8] were used; supplementary data were derived from other sources.[9]

5. Paranasal Sinuses and Mastoids (table 5): Roentgenograms of skull and face were available for all patients except 1 (case 5). Approximate standard ages for roentgenologic appearance of the various structures were compiled from the literature.[10]

B. Teeth (tables 5 and 9).—The number of erupted deciduous teeth and/or permanent teeth was counted in each child independent of degree of eruption. The number of erupted permanent teeth was used as an indicator of "dental eruption age," taking Cattell's normal means for standards.[11] For the study of the development of dental roots and unerupted crowns, dental films were available for 3 children (cases 1, 2 and 4, fig. 7) and ordinary roentgenograms of the skull for 3 (cases 3, 5 and 6). "Dental age by roentgenogram" was assessed according to the usual dental charts.[12]

C. Mental Status and Socioeconomic Background.—The revised Standard-Binet and Kuhlmann technics and standards were used for an estimation of intelligence quotient and mental age of each child. To one child (case 2), a formal personality test was given with the projective technic. In the other children, an informal

8. (*a*) Hodges, P. C.: An Epiphyseal Chart, Am. J. Roentgenol. **30**:809, 1933. (*b*) Todd, T. W., and others: Atlas of Skeletal Maturation: I. The Hand, St. Louis, C. V. Mosby Company, 1937.

9. (*a*) Davison.[4] (*b*) Krogman, W. M.: The Skeleton in Forensic Medicine (Richard Herman Jaffé Memorial Lecture), Proc. Inst. Med. Chicago **16**:154, 1946. (*c*) Flory, C. D.: Osseous Development in the Hand as an Index of Skeletal Development, Monograph of the Society for Research in Child Development, 1936, vol. 1, no. 3. (*d*) Holt, L. E., Jr., and Howland, J.: Holt's Diseases of Infancy and Childhood, revised by L. E. Holt Jr., and R. McIntosh, ed. 11, New York, D. Appleton Century Co., 1939. (*e*) Mitchell-Nelson Textbook of Pediatrics, edited by W. E. Nelson, ed. 4, Philadelphia, W. B. Saunders Company, 1945. (*f*) Camp, J. D., and Cilley, I. L.: Normal Development of Roentgenologically Important Bones and Epiphyses, Am. J. Roentgenol. **26**:905, 1931.

10. Davison.[4] Krogman.[9a] Maresh, M. M.: Paranasal Sinuses from Birth to Late Adolescence, Am. J. Dis. Child. **60**:55 (July) 1940.

11. Cattell, P.: Dentition as a Measure of Maturity, Cambridge, Mass., Harvard University Press, 1928.

12. Schour, I., and Massler, M.: Development of Human Dentition [Chart], ed. 2, Chicago, American Dental Association, 1944.

evaluation of their personalities was made by clinical and psychologic observers. Data on socioeconomic backgrounds were obtained through routine histories, supplemented for 3 children (cases 1, 4 and 6) by home visits and social workers' studies.

D. Sexual Characteristics (tables 6 and 7).—Reference is made to the patients' photographs presented in the first publication and to figure 8. In the tables, degrees of sexual maturation were indicated either by measurements of organs or by the following symbols: female breast, (+) = budding of nipples and breasts, ++ and +++ = spherical breasts with protrusion of the areolas, corresponding to stages 1 to 4 [13]; pubic and axillary hair, (+) = unpigmented down, + = a few long uncurled hairs, ++ = many pigmented curled hairs, +++ = full escutcheon with horizontal delineation, ++++ = same, extending to linea alba. The four first-named stages of pubic hair development correspond to stages 2 to 5 [13] and stages 1 to 4 [14] in the female and to maturity groups II to V [15] in the male. Normal standards for size of primary sexual organs are cited in table 7 for the male [16] and in table 8 for the female.[17] Pelvic development in the female was assessed according to the standards cited previously.[5c] Computations of the normal average sequence in age of appearance of sexual characteristics in either sex were presented in an earlier publication.[18]

E. Hormones, Metabolism and Blood.—The findings on the patients and normal standards according to age for urinary excretion of the sex hormones were presented in table 2 of the first publication.[1] Basal metabolic rates (table 1 [1]) were calculated for both chronologic and biologic ages according to the standards of the Mayo Clinic and/or Shock.[19b] Figures for urinary excretion of creatine and creatinine were compared with the normal standards tabulated by Macy.[20] Normal

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13. Reynolds, E. L., and Wines, J. V.: Individual Differences in Physical Changes Associated with Adolescence in Girls, Am. J. Dis. Child. **75**:329 (March) 1948.

14. Stuart, H. C.: Normal Growth and Development During Adolescence, New England J. Med. **234**:666, 693 and 732, 1946.

15. Greulich, W. W., and others: Somatic and Endocrine Studies of Puberal and Adolescent Boys, Monograph of the Society for Research in Child Development, 1942, vol. 7, no. 3.

16. (*a*) Rosenstern, J.: Ueber die körperliche Entwicklung in der Pubertät, Ergebn. d. inn. Med. u. Kinderh. **41**:789, 1931. (*b*) Greulich, W. W., and others: A Handbook of Methods for the Study of Adolescent Children, Monograph of the Society for Research in Child Development, 1938, vol. 3, no. 2. (*c*) Schonfeld, W. A.: Management of Male Pubescence, J. A. M. A. **121**:177 (Jan. 16) 1943.

17. Greulich and others.[16b] Rauber, A. A.: Lehrbuch der Anatomie des Menschen, Leipzig, Georg Thieme, 1914, vol. 4. Nathanson, I. T.; Towne, L. E., and Aub, S. C.: Normal Secretion of Sex Hormones, Endocrinology **25**:851, 1941.

18. Seckel, H. P. G.: Precocious Sexual Development in Children, M. Clin. North America **30**:183, 1946.

19. (*a*) Boothby, W. M.; Berkson, T., and Dunn, H. L.: Studies of the Energy Metabolism in Normal Individuals: A Standard for Basal Metabolism, Am. J. Physiol. **116**:468, 1936. (*b*) Shock, N. W.: Standard Values for Basal Oxygen Consumption in Adolescents, Am. J. Dis. Child. **64**:19 (July) 1942.

20. Macy, I. G.: Evaluation, Nutrition and Chemical Growth in Childhood, Springfield, Ill., Charles C Thomas, Publisher, 1942, vol. 1.

hematologic standards according to age were taken from Greulich's handbook[16b] and the current textbooks of pediatrics.[9d, e]

F. Postmortem Weight and Size of Organs (table 8).—In the only fatal case (case 1, a girl 7 3/12 years of age), actual weights and sizes of various organs are listed in the table, along with normal standards for girls of the same age and for adult women,[21] in terms of both actual measurements and percentages of mean organs weights and sizes of normal adult women. Expressed in terms of Scammon's four "types of organ growth" (fig. 9*A*),[22] the patient's percentage figures were used for the construction of a graph (fig. 9*B*). The curves of the graph connect the girl's presumably normal percentage figures at 2½ years of age, the time of the onset of her disorder, with the percentage figures observed at her autopsy.

G. Biologic Ages (table 9; fig. 10).—"Biologic," "organismic" or "developmental" ages were determined in all patients by expressing anthropometric, dental, psychometric and sexual maturation data obtained at a given chronologic age (fig. 10, abscissa) in terms of years of age attained according to mean normal standards (ordinate). On the graph, all points that fall below the straight diagonal lines of mean normal maturation indicate decreased biologic age, all points that fall above them, increased biologic age.[23]

II. PRESENTATION OF DATA AND OBSERVATIONS

The observations concerning anthropologic, skeletal, faciodental, sexual, psychologic and organ maturation are, for the most part, presented in tabular form (tables 1 to 9). A series of roentgenograms (figs. 4, 5, 6 and 7) and graphic charts (figs. 1, 2, 3, 9 and 10) are added for purposes of illustration. Reference should again be made to the patients' photographs presented in the first publication.[1] Some supplementary remarks concerning the patients' dental and mental maturation follow.

A. Dental Maturation.—The hyperfeminized girl (case 1) had a normal dental development at the age of 7 3/12 years except for the appearance of the right upper first permanent bicuspid which is normally expected at about 10 years of age (fig. 7 upper). However, the corresponding deciduous molar had been extracted early, a procedure that is known to precipitate the eruption of a permanent tooth. In the boy (case 3) 3 to 4 years of age, a supernumerary right upper incisor had erupted at 7 months of age. The interspaces between the second deciduous "molars" and the maxillary tuberosity in the upper jaw and between the same teeth and the mandibular ramus in the lower jaw were decidedly increased,

21. Footnote 17. Coppoletta, J. M., and Wolbach, S. B.: Body Length and Organ Weights of Infants and Children, Am. J. Path. **9**:55, 1933.

22. Scammon, R. E.: The Measurement of the Body in Childhood, in The Measurement of Man, Minneapolis, University of Minnesota Press, 1920.

23. Wilkins, L.: The Rates of Growth, Osseous Development and Mental Development in Cretins as a Guide to Thyroid Treatment, J. Pediat. **12**:429, 1938. Olson, W. C., and Hughes, B. O.: Growth of the Child as a Whole, in Barker, R. G., and others: Child Behavior and Development, New York, McGraw-Hill Book Company, Inc., 1943.

indicating a bone growth corresponding to an estimated age of 5 to 6 years. Another boy (case 4) had lost all four deciduous central incisors and had replaced the two lower ones at the age of 5 1/12 years; there were no 6 year molars. The boy's older sister had also started shedding teeth at 5 years of age.

B. Mental Development and Socioeconomic Background.—Case 1.—At 5 3/12 years this girl had an intelligence quotient of 89, at 6 9/12 years, one of 95. Her highest scores were in manual dexterity and practical reasoning. The family was of Polish-Lithuanian Catholic peasant stock and lived in the neighborhood of the Chicago stockyards. Here, in a poor and rough environment, the girl seemed to have developed a certain toughness in approaching situations and looking out for

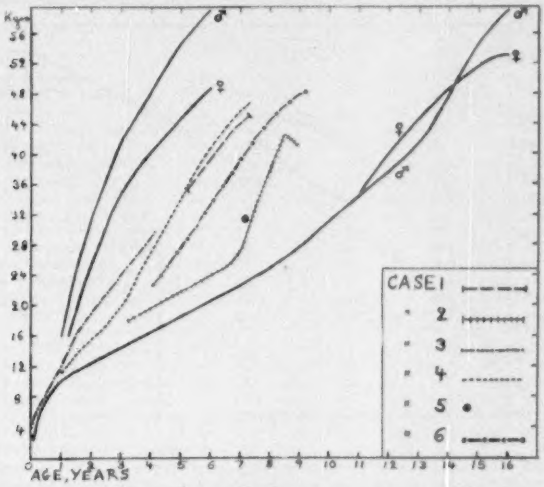

Fig. 1.—Growth curves for kilograms of body weight, cases 1 to 6. Unbroken lines at bottom represent normal curves for mean weight of boys and girls. Unbroken lines on top represent hypothetic growth curves as explained in section 1*A*, part 1.

herself. Her mother had been deserted by her husband when the child was 3 years old. He was described as cruel and probably seductive. After his desertion, the mother went to work in a factory, thus depriving her daughter emotionally and physically. The patient openly admitted hostility to her mother and seemed more attached to her grandmother, her younger brother, the nurses on the ward and the woman who was her psychiatrist. She showed both interest in and fear of men. Her anxiety at night and her initial unwillingness to undress in front of doctors was thought to be related to her parents' quarrels rather than to unconscious realization of her sexual precocity. When asked about her body size, she did not answer directly but seemed rather proud of it. However, there were no true signs of psychosexual precocity. She acted like a child of her chronologic age in every respect.

CASE 2.—This 9 year old child was the third of four boys in a Catholic family of Italian-Swedish extraction who lived in a western factory area of Chicago. The parents were born in the United States, and the father was a factory worker. In a psychometric test the boy received an intelligence rating of 79. The scatter of his scores ranged from 6 to 10 years. His performance was poorest in abstractions, digit recall and social comprehension and best in reading and recall of material read. The small vocabulary, inferior use of language and poor social comprehension seemed to reflect a low cultural background which offered little intellectual stimulation. It was, therefore, felt that the test performance was a minimal estimate of the patient's intellectual capacity. The incongruity between his actual age and his physical appearance, on the one hand, and between his physical appearance and his psychologic performance, on the other, was striking. He was shy and inhibited and did not offer any spontaneous conversation, although he

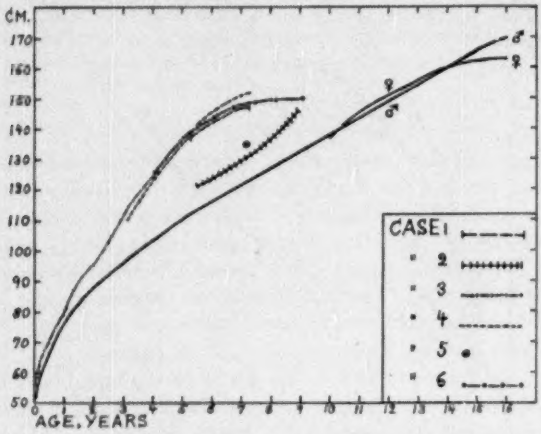

Fig. 2.—Growth curves for centimeters of standing height, cases 1 to 6. Unbroken lines at bottom represent normal curves for mean height of boys and girls.

answered direct questions readily. He had only superficial rapport with the examiner and was restless. His nails were severely bitten, and frequently during the test he made noises with his lips. Although at first he enjoyed the "new" activity, he seemed to cooperate only because he felt he had to and was more anxious to finish the test than to spend time being critical of his answers.

CASE 3.—This boy was the only child of English-American, cultured, well-to-do persons in early middle age. They operated and lived in a hotel in southern Colorado. The child behaved generally according to his chronologic age level of 3 to 4 years. He was somewhat fearful of his father and moderately aggressive. He had had almost no contact with other children. He longed for a baby brother but failed to ask questions or to show curiosity in regard to sex. In a psychometric test done at 3 years of age, the discrepancy between his bodily development and his completely infantile behavior was obvious. He was active, wiggly and untiring but easy to control. His speech was indistinct and his gait awkward.

He adapted easily to other persons and accepted restrictions unusually well. It was interesting to note that when he drew a picture of a man he elongated the arms tremendously. His test performance ranged from 4 to 7 11/12 years and was characterized by an unusually large vocabulary and good rote recall, as well as by ability to generalize. On the other hand, he had some difficulty with visual recall of pictures and with tasks involving coordination of eye and hand. He earned an intelligence rating of about 150. However, it was felt that this rating was not any higher than that obtained by a great many children who are completely normal in their physical development. At 4 years of age, he showed the same relative mental ability; his interests were all in cowboys and "funnybooks." He was strong enough to wrestle with his father.

TABLE 1.—*Anthropometric Data for Girls (Cases 1 and 5)**

	Case 1			Case 5	Normal Girls				
Age, years	5 3/12	6 9/12	7 3/12	7 2/12	5	7	10	13	14
Body weight, Kg.	35.3	42.2	44.7	31.3	18.9	22.5	31.0	40.8	48.5
Standing height, cm.	127	146	147	135	109	120	137	150	160
Sitting height, cm.	74	....	....	....	62.5	67.9	73.8	78.7	82.4
Suprasternal height, cm.	110	118	....	110	86	96	114	126	133
Acromial height, cm.	110	118	....	106	86	96	114	126	134
Symphysial height, cm.	67.8	73.5	....	67.5	52.2	60.8	71.9	79.6	84.6
Iliospinous height, cm.	73.7	80.2	....	73.7	59.5	68.4	80.3	88.6	93.5
Anterior trunk height, cm.	42	45.5	....	42.0	34.1	37.3	42.3	45.7	48.7
Anterior trunk height index	....	30.5	....	31.1	30.0	30.5	30.0	30.0	30.0
Chest circumference, cm.	68.5	....	....	....	54.3	59.2	62.9	67.9	80.3
Biacromial breadth, cm.	29.5	31.3	....	30.3	24.9	26.7	29.8	31.9	33.5
Bicristal breadth, cm.	24.3	26.9	26.8	21.8	18.2	19.6	22.3	24.4	26.1
Bitrochanteric breadth, cm.	28.4	28.6	29.8	23.8	19.6	21.5	24.7	27.9	30.9
Trunk breadth index	....	88.0	....	71.9	73.6	73.4	75.4	76.4	77.9
Head circumference, cm.	50	....	....	....	51.3	52.1	52.7	53.3	55.6
Head length, cm.	17.0	17.1	17.2	16.8	17.6	17.9	18.2	18.5	18.5
Head breadth (biparietal) cm.	15.2	15.2	15.4	14.9	13.9	14.1	14.4	14.6	14.6
Cephalic index	....	88.5	....	88.7	79.1	79.2	79.3	79.1	79.2
Face height, cm.	9.5	9.4	9.7	10.4	9.7	10.1	10.5	10.9	11.2
Face breadth (bizygomatic), cm.	12.7	13.0	13.1	12.5	11.3	11.6	12.3	12.6	13.8
Facial index	....	73.3	....	83.2	86.1	85.3	85.4	86.2	87.6

* Terms are explained and sources of normal mean standards are indicated in section I A, parts 1, 2 and 3. The weight at birth in case 1 was 2,550 Gm., and in case 5, 2,709 Gm. See figures 1, 2 and 3.

CASE 4.—The patient was the second of three children and the only boy in a typical midwestern family. His father was a manual worker and small businessman. At 3 2/12 years of age, two attempts to give a psychometric test were unsuccessful because of the child's shyness and inhibition. In a third trial he finally broke silence and told a story of a trip he had made. He was considered to have low average intelligence (intelligence quotient, 91). At 5 1/12 years of age, the contrast between his adolescent appearance and his dull, completely childlike behavior was spectacular. No formal test was done at that age. He knew how old he was but did not know his birthday. He counted his fingers correctly up to five but was unable to give his address. A few weeks previously he had been refused admission to public kindergarten because he was too young! He had never asked any questions related to sex. His psychosexual behavior was alto-

TABLE 2.—*Anthropometric Data for Boys (Cases 2, 3 and 4)* *

	Case 2	Case 3		Case 4	Normal Boys				
Age, years	8 11/12	3 2/12	4 1/12	7 3/12	3	6	9	12	14
Body weight, Kg.	41.1	25.0	29.6	46.7	14.3	20.8	27.8	34.5	48.0
Standing height, cm.	140	114.5	125.5	152	96	116	133	149	160
Arm span, cm.	146	112	125	149	96	113	....	141	151
Sitting height, cm.	79.2	68.8	72.5	85	57.6	65.8	72.9	77.6	82.9
Suprasternal height, cm.	115	89.2	97.3	121.5	74	92	109	123	135
Acromial height, cm.	115	86.7	97.2	120.5	74	90	108	122	135
Symphysial height, cm.	69.4	51.5	58.0	74	42.8	56.3	67.3	77.4	85.6
Iliospinous height, cm.	84.2	63.0	65.5	83.2	49.3	65.6	75.5	86.8	95.4
Anterior trunk height, cm.	45.6	37.7	39.3	47.6	30.5	36.0	41.3	45.5	48.9
Anterior trunk height index	39.5	32.9	31.3	31.3	31.9	30.7	30.3	30.3	30.0
Chest circumference, cm.	79	60	60	71.5	50.3	59.0	62.2	68.6	76.8
Chest depth, cm.	17.5	15.0	15.6	16.4	12.7	14.4	15.7	17.0	18.1
Chest breadth, cm.	24.4	19.2	21.0	23.6	17.2	19.7	21.0	23.8	25.4
Biacromial breadth, cm.	34.6	26.6	28.5	35.0	22.6	25.9	29.2	31.9	34.4
Bicristal breadth, cm.	23.3	19.5	21.3	23.5	15.9	19.3	21.5	23.6	25.4
Bitrochanteric breadth, cm.	27.2	22.5	23.4	28.4	17.5	20.3	23.2	26.4	29.3
Trunk breadth index	67.4	73.3	74.7	67.1	70.6	74.1	73.7	74.3	74.0
Head circumference, cm.	56.2	55	55.5	52.7	50.8	52.3	53.0	54.0	56.3
Head length, cm.	19.8	19.5	19.3	17.4	17.2	18.1	18.5	18.8	19.0
Head breadth (biparietal), cm.	14.7	15.3	15.1	15.3	14.1	14.3	14.6	14.8	14.9
Cephalic index	74.2	77.9	78.2	87.3	82.7	79.3	78.9	78.9	78.7
Face height, cm.	11.5	9.4	10.9	11.3	8.8	9.9	10.5	11.0	11.5
Face breadth (bizygomatic), cm.	12.4	12.2	12.2	12.9	11.3	11.6	12.2	12.7	13.0
Face depth, upper, cm.	9.2	....	8.5	8.9	8.0	....	8.8	9.1	9.2
Face depth, middle, cm.	....	....	8.9	8.5	7.9	....	8.8	9.1	9.3
Face depth, lower, cm.	10.5	....	9.8	10.5	8.7	....	10.1	10.5	10.8
Facial index	92.8	77.0	80.3	82.2	83.5	85.1	85.9	86.9	88.4

* Terms are explained and sources of normal mean standards indicated in section I4, parts 1, 2 and 3. In case 2, at birth, 3, 5½, 7½, and 8½ years of age, height was 53, ? (no data), 121, 139.5 and 142 cm., and weight was 4,540 Gm. and 18.0, 22.7, 33.6 and 42.6 Kg., respectively; both parents were only 5 feet (152 cm.) tall. In case 3, at birth, ¼, 1, 1½, 2 and 2 7/12 years of age, height was 50, 70, 79, 90, 95.5 and 105 cm., and weight was 4,400 and 8,000 Gm. and 11.9, 16.2, 18.9 and 21.6 Kg., respectively. For previous data on case 4, see table 3. The Broadbent cephalometric technic was used in cases 3 and 4, measurement for cutaneous outlines being listed in this table. See figures 1 and 2.

TABLE 3.—*Anthropometric Data for Boy (Case 4) and Girl (Case 6)* *

	Case 4			Case 6	
Age, years	3 2/12	3 7/12	5 1/12	4 1/12	9 2/12
Body weight, Kg.	20.8	23.9	34.5	22.7	48.2
Standing height, cm.	110	117	137	125	150
Arm span, cm.	108	114	135	....	154
Symphysial height, cm.	....	....	....	59.5	71
Chest circumference, cm.	62	....	66	....	79
Head circumference, cm.	49	50	51	48.5	52

* For normal averages, consult tables 1 and 2. In the boy (case 4) more measurements were done at 7 3/12 years of age (table 2); the boy's body weight at birth, 1 year and 2½ years was reported as 3,200 Gm., 11.3 Kg. and 17.3 Kg., respectively. In the girl (case 6) the weight at birth was given as 2,950 Gm. The data at 4 1/12 years of age were contributed by the Cook County Hospital, Chicago. See figures 1 and 2.

gether on the level of an ordinary 5 year old child. When 7¼ years old, he still displayed an infantile behavior but was bashful and conscious of his size. He attended second grade in school and was a low average student.

Case 5.—This girl was the second of three children of middle-aged Chicago-born parents who lived and worked in the stockyard's neighborhood. The girl's mental development was reflected in an intelligence quotient of 102. Her behavior was ordinary for a 7 year old girl, particularly in regard to psychosexual maturation, which was completely infantile.

Case 6.—"Richard," 9 years of age, was the only child of a 29 year old woman who was born in Chicago of German parents and who lived and worked in the stockyard area. Her first husband, the child's father, had been of Italian

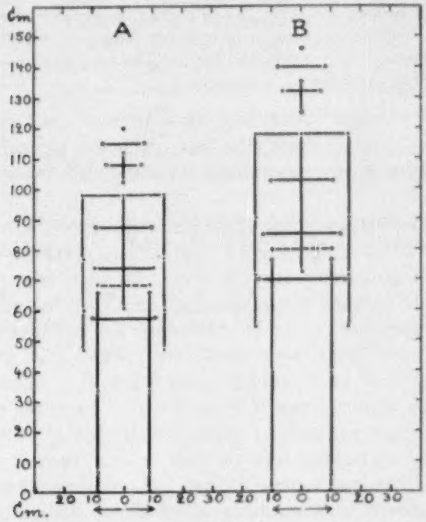

Fig. 3.—Schematic representations of body frames as obtained by linear and transverse anthropometric measurements. *A*, average normal girl, aged 7 years, based on figures derived from literature. *B*, hyperfeminized girl (case 1), aged 6 9/12 years, based on figures of table 1 (arm and leg measurements added on graph). Solid lines and dots indicate height, length and breadth as actually measured; broken lines and dots, height above floor actually measured but breadth estimated, and solid lines and circles, breadth and height actually measured but height above floor estimated.

background and had blamed her for the child's abnormality. He finally deserted her. The second husband, whom she had married only recently, was a 19 year old serviceman of Polish descent. The stepfather and patient seemed to be fond of each other, while there was little warmth toward the child on the mother's part. The patient entered a boarding school for mentally retarded children at the age of 7 and changed to an ungraded class in public school at 9 years. A formal psychometric test done at this time showed dull average intelligence (intelligence

quotient, 86) which seemed to be commensurate with third grade placement in school. Successes ranged between the 6 and 9 year levels. Memory was above average, while reasoning ability and integration of thought processes were two years below average and were characterized by confusion. Verbalization was laborious and the quality of his words was inferior. Emotionally, the patient appeared to be a friendly and cooperative child who was restless, shifting, distractable, insecure and ill at ease. However, in a psychiatric interview, the child did not show as much anxiety as was expected in the circumstances. "He" expressed considerable sensitivity about the stares of his schoolmates in the locker room at swimming time and about "his" inability to urinate in the standing position like other boys. When it was explained that he was growing faster than the other boys and had the development of a man, he protested resentfully, "I don't want to be grown up, I am still a boy." After laparotomy for castration, he was disappointed that nothing had been done to correct his feminine manner of urination. However, he did not want to have it corrected now. Nothing was said to the child of his true sex. Aside from the childlike masculine sex consciousness, there was complete psychosexual immaturity.

One of the patients' outstanding characteristics was their precocious macrosomia, i. e., the increase over that which was normal for chronologic age in their skeletal dimensions, fat and muscle mass and visceral weight.

Once the underlying disorder had started, curves for weight and height (tables 1 and 2; figs. 1 and 2) fell well above the curves for mean normal growth of contemporary children. This was true regardless of the nature of the patients' sexual precocity, be it hypothalamic or adrenocortical. Weights were ahead of chronologic age by three to six years and heights by one and a half to five years. When onset of the disease came early in life, as in 2 patients (cases 3 and 4), midinfancy growth rates continued up to the age of 4 and 5 years. Later on, their growth curves ran parallel to, or were directly continued by, other patients' growth curves that had not been recorded earlier (cases 1, 3, 4 and 6). By the age of 7 to 9 years, some children had reached adolescent size and a decreased growth rate, auguring shortness of stature in adult life. When viewed as a whole, the patients' curves for growth lay midway between normal children's curves and those hypothetic curves (fig. 1) which indicate the manner in which children would grow provided they jumped from infancy into adolescence after the fashion of most higher vertebrate animals.[8] Macrosomia was further indicated by the adolescent type of feminine deposition of body fat in the hyperfeminized girl (case 1) and by the considerable postmortem overweight of her "general" and "lymphoid" types of organs (table 8; fig. 9). Similarly, in the boys (cases 2 and 4; fig. 8), the adolescent type of masculine muscle development was in evidence and the adolescent rate of urinary creatine-creatinine excretion was demonstrated, as considered later in this paper.

Other somatometric studies (tables 1 to 3; fig. 3) confirmed the impression of a roughly proportionate macrosomia. Advances over

chronologic age ranged from two to seven years. The arm span was within 3 to 4 cm. of the standing height. The anterior trunk height (suprasternal notch to symphysion) was comparatively great and the anterior trunk height index relatively low, indicating somewhat infantile proportions. Such relative preponderance of linear growth of the trunk

TABLE 4.—*Maximum Skeletal Ages, in Years, by Skeletal Provinces for All Cases* *

	Case 1 Female		Case 2 Male,	Case 3 Male		Case 4 Male			Case 5 Female,	Case 6 Female	
Chronologic age, years....	5 2/12	7 2/12	8 11/12	3 2/12	4 1/12	3 2/12	5 1/12	7 2/12	7 2/12	4 1/12	9 2/12
Spine and shoulder girdle.	10	15 to 17	..	<10	..	<10	10	15	14 to 15	..	17 to 18
Elbow	8	14 to 16	12 to 14	< 7	8 to 9	7 to 8	..	16	14 to 15	..	16 to 17
Wrist and hand.....	9¾ to 11¾	15½ to 17	15 to 16	6 to 7	10¼	10½	12¾	16	12¾	6	..
(Todd [8b] no.).....	(12 to 25)	(33 to 35)	(34)	(16)	(23)	(22)	(38)	(35)	(30)	..	..
Pelvis and hip.....	10	14 to 16	14 to 16	<10	10	10	13 to 14	15	14	..	18
Knee	..	<17	<17	..	..	..	11	..	>11	11	18
Ankle and foot.....	..	14	<15	..	10	..	..	14	14 to 15	..	14 to 15

* Blank spaces indicate information was unavailable or noncontributory. See figures 4, 5 and 6.

TABLE 5.—*Maturation of Mastoids, Paranasal Sinuses, Spheno-Occipital Juncture and Teeth* *

	Case 1			Case 2	Case 3		Case 4			Case 5	Case 6		Mean Normal Age, Yr., Mastoids and Sinuses
Age, years.....	5 2/12	6 9/12	7 2/12	8 10/12	3 2/12	4 1/12	3 2/12	5 1/12	7 2/12	7 2/12	4 1/12	9 2/12	
Mastoid.....	+	....	+++	++	+	++	....	....	....	....	....	+++	Ca. 3
Sphenoid.....	+	++	+++	+	0	0	+	+	++	....	....	+	Ca. 3 to 5
Frontal.....	0	0	0	0	+	+	+	++	++	....	....	0	Ca. 7 to 9
Spheno-occipital juncture.....	Not seen	Not seen	Not seen	Not seen	Open	Open	....	Open	....	....	....	Open	Usually closed, 17 to 20 years
Erupted teeth, deciduous: permanent..	15:1	15:6	12:10	6:14	21:0	21:0	20:0	16:2	12:12	12:12	20:0	0:24	

* All but dental data refer to roentgenographic appearances. 0 indicates absence of sinuses or, in the case of the frontal sinuses, that they were not raised above the level of the orbital roofs. Plus signs indicate presence and increasing size of sinuses. Blank spaces show that no information was available. Maxillary sinuses were present in all patients (they normally appear at 6 to 12 months of age). The coronal suture was open in one patient (case 6) at 9-2/12 years (it is usually not closed before the thirtieth year). See figure 7.

was also described by other observers.[24] When comparisons were made between linear and transverse body dimensions, the latter were more advanced than the former. For instance, in the virilized children (cases

24. (*a*) Heuyer, G., and Vogt: Un cas de macrogénitosomie précoce, Arch. de méd. d. enf. **33**:737, 1930. (*b*) Thoms, H., and Hershman, A. A.: A Case of Sexual Precocity, Am. J. Obst. & Gynec. **6**:349, 1923. (*c*) Mattar, A.; Correa, B., and Urrutia, V. C.; Early Sexual Development, with Report of Two Cases Rev. Chilena de pediat. **17**:305, 1946.

2 to 5), shoulder breadth was up to two and a half years more progressed than height. On the other hand, in the hyperfeminized girl (case 1)

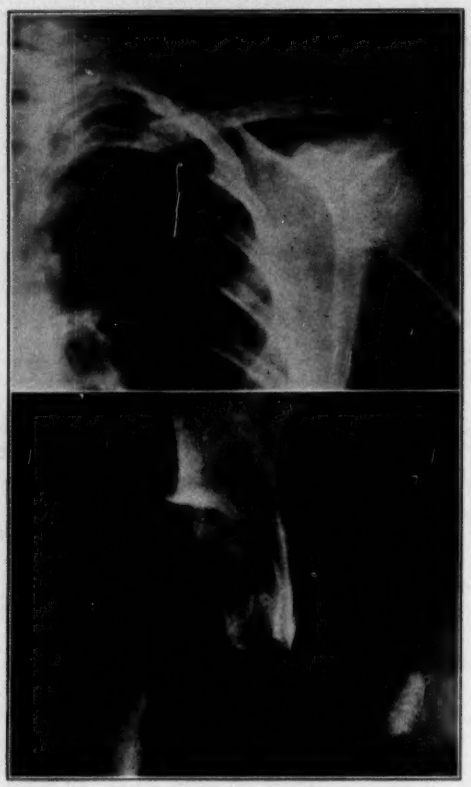

Fig. 4.—Upper, roentgenogram of girl (case 1) at 6 9/12 years of age. Note presence of the epiphyses to the acromion and coracoid process, expected to appear normally at 11½ to 14 and at 15 years, respectively. The epiphysis to the medial end of the clavicle, not seen in the roentgenogram, was fusing with the shaft on microscopic examination, indicating a still higher bone age. Lower, roentgenogram of boy (case 2) at 8 10/12 years of age. Note presence of epiphysis of the ischiac tuberosity, expected at 14 to 15 years, and considerable fusion of the epiphysial line of the femoral head (and both trochanters?), expected to be complete at 16 to 17 years.

pelvic diameters were ahead of standing height by about two and a half years. Between 5 and 7 years of age, her bicristal breadth had increased from 24.3 to 26.8 cm. and her bitrochanteric breadth from 26.4 to 29.8

cm. In absolute, as well as incremental, terms these figures corresponded closely to those of a normal girl's pelvic growth between 12 and 14 years of age. Similarly, trunk breadth indexes (bicristal breadth/biacromial breadth) were unusually high (83 per cent) in the girl (case 1) and unusually low (67 per cent) in the boys (cases 2 and 4). In other words, normal female and male adolescent proportions were exaggerated in these precocious children. The pelvimetric studies of Thoms, of Gesell's group,[25] were not made early enough in the course of the girl's illness to be of great significance. In Gesell's patient betwen 4 and 17 years of age cranial length and breadth were reported to have increased according to chronologic norms. This was only partially true of the present patients (tables 1 to 3). Chronologic age levels were maintained by length and circumference of the head in 3 (cases 1, 4 and 5), by circumference of the head in 1 (case 6) and by breadth of the head in 1 (case 2). The remaining cephalic measurements were above chronologic level in 5 (cases 1 to 5); all measurements were precocious in one boy (case 3). Two children (cases 1 and 4) had medium-sized, relatively short, but broad, heads with a high cephalic index; 2 (cases 2 and 3) had large, high and rather narrow heads with a low cephalic index. The spheno-occipital juncture was open whenever visualized (table 5). The hyperfeminized girl's brain (case 1) was 100 Gm. overweight for her age and had attained normal adult size. Large as many of these cephalic dimensions may appear, it must be kept in mind that the brain and skull grow slowly after 6 years of age, when they reach about 90 per cent of final adult size, and that their growth and configuration are largely determined by hereditary and familial factors.

As for facial dimensions (tables 1, 2 and 9) the precociously feminized girl (case 1) had a low but broad face with an extremely low, infantile facial index. Between the ages of 5 and 7 years, her facial growth on classic cephalometry was virtually at a standstill in spite of rapid growth in other parts of the body. In contrast to this, the other 5 patients, all virilized boys or girls, showed an advancement of facial growth for chronologic age on clinical (case 6), as well as cephalometric, observation (cases 2 to 5). Biologic ages for their facial height (table 9) were from three to seven years ahead of chronologic ages and those for facial breadth and depth were also advanced. The dynamic progress in facial height between 3 and 4 years of age in one boy (case 3) was particularly noteworthy when compared with the static condition of facial height between 5 and 7 years of age in the hyperfeminized girl (case 1). Precocious development of jaws and facial skeleton were

25. Gesell, A.; Thoms, H.; Hartman, F. B., and Thompson, H.: Mental and Physical Growth in Pubertas Praecox: Report of Fifteen Years' Study of Case, Arch. Neurol. & Psychiat. **41**:755 (April) 1939.

described in the literature in a 2 year old girl with hamartoma of the tuber cinereum [26] and in a 4½ year old boy with adrenogenital syndrome.[27]

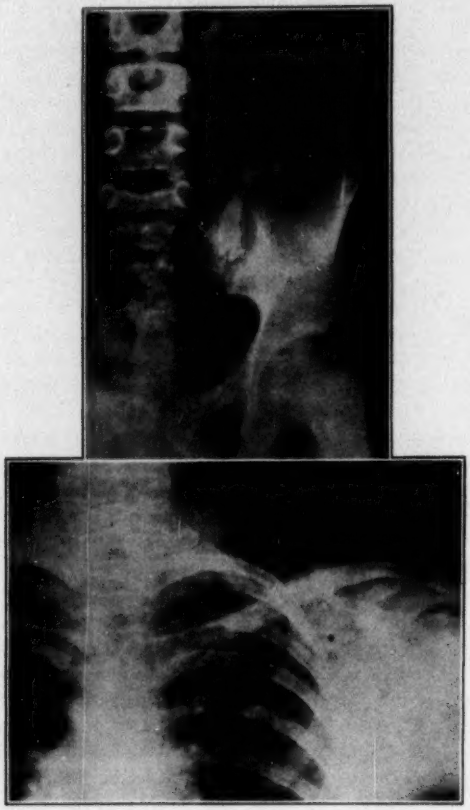

Fig. 5.—Upper, roentgenogram of boy (case 4), aged 5 1/12 years. Note presence of epiphysis to the iliac crest, expected at 13½ to 14 years of age. Lower, roentgenogram of genetic girl (case 6) at 9 2/12 years of age. Note presence of epiphysis to the medial end of the clavicle, due to appear at 17 years.

26. Bronstein, I. P.; Luhan, J. A., and Mavrelis, W. B.: Precocious Puberty Associated with Hyperplastic Abnormality of Tuber Cinereum, Am. J. Dis. Child. **64**:211 (Aug.) 1942; correction, ibid. **64**:723 (Oct.) 1942.

27. Schour, I., and Massler, M.: Endocrines and Dentistry, J. A. Dent. A. **30**:595, 763 and 943, 1943.

Turning from anthropometric problems to the study of teeth and paranasal sinuses, observations tended to show that dental maturation was but slightly, if at all, advanced over the chronologic age of these patients (tables 5 and 9; fig. 7). Dental age was within about a year of chronologic age in all children except 1 (case 6) whose progress amounted to about two years. When dental development was compared

Fig. 6.—Roentgenograms of genetic girl (case 6). Upper, note calcification of cartilages of lower ribs which is normally not seen before 20 years, and then infrequently. Lower, note calcification of pineal body not indicative of a pineal tumor but of patient's "biologic age."

with that of the jaws and face, conformity was found only in the hyperfeminized girl (case 1), whereas in the 5 virilized children the teeth appeared to be lagging behind the jaws by several years. The contrast between dental and bony development was even greater when com-

parisons were made between dentures and skeletal maturation in general: All patients 4 to 9 years of age still had all or part of their deciduous teeth when their skeleton was advanced to the age of 11 to 16 years, i. e., an age at which normally no deciduous teeth are present any longer.

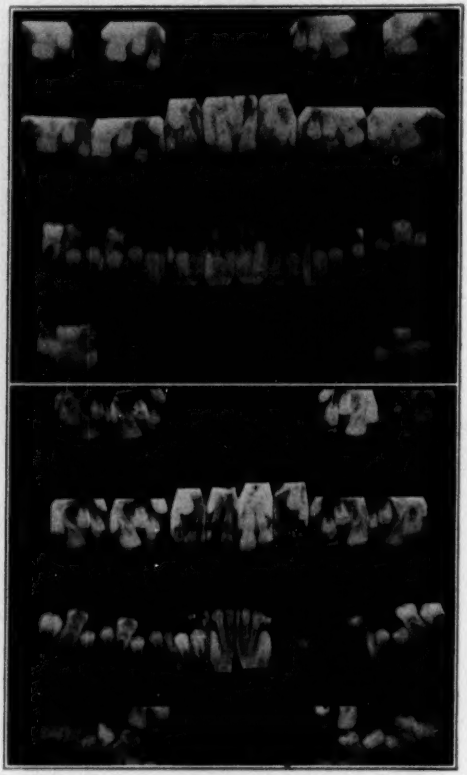

Fig. 7.—Upper, dental roentgenograms of girl (case 1) aged 7 3/12 years. The pictures indicate a dental age of about 7¾ years. The upper left permanent premolar had erupted prematurely due to early loss of the corresponding deciduous "molar." There were 12 deciduous teeth. Lower dental roentgenograms of boy (case 2), aged 9 3/12 years. They indicate a dental age of about 10 years. Note presence of 6 deciduous teeth.

The literature on dental development in children with sexual precocity is both scanty and confusing. Broad statements concerning "premature eruption" and "early dentition," sometimes with reference to pineal tumors and the Albright-McCune-Sternberg syndrome (osteitis fibrosa

cystica), have been made.[28] On the other hand, detailed reports were published to the effect that dental age was either normal or not more than one-half year to two years ahead of chronologic age.[29] Wide spacing of deciduous teeth in the jaws was also mentioned.[30] An unpublished survey of the literature on testicular, ovarian and adrenocortical neoplasms associated with sexual precocity which I undertook years ago had led to the same conclusion, if two extravagant claims of advanced dental ages were discarded.[31] Schour and Massler [27] stated in regard to a patient of Bronstein with the adrenogenital syndrome:

> The development of the cranial and facial skeleton and the paranasal sinuses follows in general the growth of the rest of the skeletal system. . . . The size of the jaws appears to be in harmony with the rest of the craniofacial skeleton.
>
> The apposition of enamel and dentin and the eruption [of teeth] are accelerated but not to the same degree as is skeletal growth. . . . Peculiarly enough, tooth development . . . is much less affected than is skeletal development.

In conditions roughly opposite to sexual precocity, such as certain cases of hypopituitary dwarfism with infantilism and, even, of cretinism in man,[32] or of the status following hypophysectomy in rats,[33] tooth size and crown development may also be less affected than the rest of the

28. Chamberlain, I. M.: Precocious Puberty, Am. J. Dis. Child. **45**:215 (Jan.) 1933. Reuben, S., and Manning, G. R.: Precocious Puberty, Arch. Pediat. **39**:769, 1922; **40**:27, 1923. Lichtwitz, L.: Role of Endocrinology in Orthodontics, Am. J. Orthodontics **24**:1009, 1938. Levy, M. D.: The Influence of the Endocrines on the Teeth and Jaw, ibid. **26**:671, 1940.

29. Gesell and others.[28] Bronstein and others.[26] Schour and Massler.[27] Le Marquant, H. S., and Russell, D. S.: A Case of Pubertas Praecox (Macrogenitosomia Praecox) in a Boy, Associated with a Tumour in the Floor of the Third Ventricle, Roy. Berkshire Hosp. Rep., 1934, p. 31. Weinberger, L. M., and Grant, F. C.: Precocious Puberty and Tumors of the Hypothalamus, Arch. Int. Med. **67**:762 (April) 1941. Taft, L. L.: Dental Findings in Five-Year Old Peruvian Mother, New York J. Dent. **11**:225, 1941. Cross, S.: Endocrines: Their Relation to Orthodontic Diagnosis and Treatment Planning, Am. J. Orthodontics **34**:418, 1948.

30. Rowe, A. W., and Lawrence, C. H.: Studies on the Endocrine Glands: IV. The Male and Female Gonads, Endocrinology **12**:591, 1928.

31. (*a*) Linser, P.: Ueber die Beziehungen zwischen Nebennieren und Körperwachstum, besonders Riesenwuchs, Beitr. z. klin. Chir. **37**:282, 1903. (*b*) Gordon, M. B., and Browder, E. J.: Suprarenal Carcinoma with Pubertas Praecox in a Boy Three Years of Age, Endocrinology **11**:265, 1927.

32. (*a*) Cohen, M. M., and Wagner, R.: Dental Development in Pituitary Dwarfism, J. Dent. Research **27**:445, 1948. (*b*) Unpublished observations. (*c*) Schour and Massler.[27] (*d*) Schour, I.; Brodie, A. G., and King, E. Q.: The Hypophysis and the Teeth: IV. Dental Changes in Hypopituitary Condition: Case Report, Angle Orthodontist **4**:285, 1934.

33. Schour, I.: The Hypophysis and the Teeth, Angle Orthodontist **4**:3, 1934; II. Effects of Replacement Therapy on Eruption and Histologic Changes of Teeth of Hypophysectomized Rat, ibid. **4**:142, 1934; III. Changes in Rat Molar Following Hypophysectomy, ibid. **4**:205, 1934.

body, including the jaws. "The maxilla, mandible, and teeth have their individual and independent growth patterns. . . ." [32a]

TABLE 6.—*Sexual Maturation of Girls (Cases 1, 5 and 6)* *

	Case 1				Case 5		Case 6		
Age, years	3	5 3/12	6 9/12	7 3/12	5	7 9/12	4 1/12	6 to 8	9 2/12
Breast development	(+)	++	+++	+++	0	0	0	0	0
Menstruation	+	+	+	+	0	0	0	0	0
Pubic hair	0	(+)	+	+	+	+++	+	++	+++
Axillary hair	0	0	+	+	0	+	0	+	++
Terminal hair	..	0	0	0	0	+	0	0	+
Facial hair	..	0	0	0	0	+	0	(+)	+
Facial acne	..	0	0	0	0	+	0	0	+
Deep voice	..	0	0	0	+	+	0	(+)	+
Length of clitoris, cm.		Normal			>	3 × 1.5	4	..	5
Size of uterus, cm.	..	..	..	7 × 3.5	..	3 × 2	..	..	3 × 2
Size of ovary,									
Gm.	..	..	..	Ca. 5	..	Infantile	..	..	..
cm.	..	..	..	Ca. 2.5 × 1.5	..	Infantile	..	..	2.5 × 1

* Plus signs indicate presence of character, 0, its absence and > increased. Blank spaces mean no information was available. For degrees of maturation and normal mean size of uterus and ovary, see part II*D* and table 8. Data were taken from the histories, in case 1 for 3 years of age, in case 5 for 5 years of age and in case 6 for 6 to 8 years of age. In case 6, data for 4 1/12 years of age were submitted by the Cook County Hospital, Chicago. In case 1, breast development started at 2½ years, menarche occurred shortly after the third birthday. In case 5, a large clitoris was noted at birth, a husky voice at 1 year and pubic hair at 5 years. In case 6, a "hypospadias with undescended testicles" was assumed from birth and pubic hair was first observed at 3 years of age. See photographs of patients.[1]

TABLE 7.—*Sexual Maturation for Boys (Cases 2, 3 and 4)* *

	Case 2			Case 3			Case 4		
Age, years	7 7/12	8 6/12	8 11/12	2 7/12	3 2/12	4 1/12	3 2/12	5 1/12	7 3/12
Pubic hair	+++	+++	++++	0	(+)	+	++	+++	+++
Axillary hair	0	0	+	0	0	0	0	+	+++
Terminal hair	++	++	+++	0	0	0	0	+	++
Facial hair	0	+	++	0	0	0	0	+	++
Facial seborrhea	0	0	+	0	0	0	+	+	++
Facial acne	0	0	+	0	0	0	0	+	++
Deep voice	+	+	++	0	0	0	0	+	++
Budding of mamilla	..	+	+	0	0	+	0	0	0
Enlargement of prostate	+	++	++	..	0	..	..	..	..
Length of penis, cm.	>	>	8	7	6.5	7	9.5	12.5	12.5
Circumference of penis, cm.	>	>	11	7	8.5	9	8.5	8.5	10.5
Length × width of testes, cm.	>	>	5 × 3	3	4 × 2.5	4.5 × 2.5	<2	2	2.5 × 1.5

* Plus signs indicate the presence and 0 the absence of characters. > means increased, <, decreased, and blank spaces, no information available. Normal mean size of penis in length is: at 1 to 10 years, 3 to 4 cm. and at 14 to 16 years, 8 to 15 cm., and in circumference: at 1 to 12 years, 3.5 to 4 cm. and at 14 to 16 years, 7.5 to 9 cm. Normal average size of testes is: at 1 to 12 years, 1.6 by 0.65 cm.; at 12 to 16 years, up to 3.5 by 1.4 cm., and in the adult, 4 to 5 by 2.5 to 3.5 cm. (See footnotes 14 to 17.) In case 2, genital enlargement, pubic hair and deep voice were noticed at about 6½ years and facial hair shortly after 8 years of age. In case 3, the genitalia appeared excessively large between 1¼ and 2 years; pubic down was noticed shortly before 3 years of age. In case 4, the penis was said to be enlarged from birth; pubic hair was first noticed at 2 11/12 years and axillary hair shortly before 5 years. At 3 2/12 years of age the erect penis measured 14 cm. in length dorsally. See photographs of patients [1] and figure 8.

The mastoid cells and sphenoid sinuses (table 5) were normal in size for chronologic age in all the children of this series. The frontal sinuses behaved paradoxically: They were rudimentary between 7 and 9 years in 3 children (cases 1, 2 and 6) and well developed between 3

and 5 years in 2 (cases 3 and 4). In Bronstein's 2 patients [34] maturation of paranasal sinus was reported to be advanced.

Another of the patients' outstanding characteristics was their precocious skeletal maturation (tables 4 and 9; figs. 4, 5, 6 and 10). Their skeletal age was from two to three times their chronologic age, i. e., adolescent levels of skeletal maturity were attained at 5 to 7 years and young adult levels at 9 years of chronologic age. In individual children, skeletal progress over periods of 1, 2, 4 and 5 calender years amounted to 1 to 4, 2½ to 7, 5 to 8 and 7 biologic years,

Fig. 8 (case 4).—Boy aged 7 3/12 years. This is the same patient as shown in figure 8 of the first publication [1] at the ages of 3 2/12 and 5 1/12 years. Note fully adolescent appearance, including muscle development, terminal hair, facial hair and acne.

respectively. Varying degrees of epiphysial fusion of the femoral head and ankle bones were observed between 7 and 9 years, permitting a prognosis of impending growth arrest and low adult stature. Maturational progress in the six major areas of the skeleton (table 4) was fairly uniform, although differences in levels of one to three years did occur; within a single major area uniformity was greater (± 1 year). Epiphysial maturation of the long bones as compared with

34. Bronstein and others.[26] Schour and Massler.[27]

that of the small ones (girdles, wrists, ankle) was more advanced in 3 children (cases 1, 2 and 5), less advanced in 2 (cases 3 and 4) and equal in 1 (case 6). Spectacular precocity of skeletal maturation had been almost unanimously reported in the literature on sexual precocity ever since Ogston [35] observed calcified ribs at autopsy in a child with the adrenogenital syndrome and Linser [21a] first demonstrated carpal advancement by roentgenogram in a similar patient, a boy aged 5½ years.

For the purpose of discussing the patients' precocious sexual maturation, the only patient with hyperfeminization due to hypothalamic

TABLE 8.—*Postmortem Weight or Size of Organs for Hyperfeminized Girl (Case 1)* *

	Organ Weight or Size, Absolute			Organ Weights in Percentage of Mean Normal Adult Weights	
	Patient	Mean Normals, Females		Patient	Normal Girls
Age, years	7 3/12	7	20 to 30	7 3/12	7
Body weight, Kg.	44.7	27.6	55.0	81	41
Heart, Gm.	190	100	275	73	36
Lungs (both), Gm.	500	253	650	77	26
Liver, Gm.	1,070	680	1,500	71	45
Pancreas, Gm.	55	...	90	61	..
Kidneys (both), Gm.	210	139	300	70	23
Spleen, Gm.	300	66	150	200	44
Thymus, Gm.	50	20	20	250	145
Uterus, size, cm.	7 × 3.5	3.1	7.5 × 5	Ca. 90	Ca. 40
Ovary (one), size, cm.	Ca. 2.5 × 1.5?	...	5 × 2	Ca. 50?	..
Ovary (one), weight, Gm.	Ca. 5	1.5	5 to 10	Ca. 66	Ca. 10
Brain, Gm.	1,350	1,263	1,350	100	93
Pituitary, Gm.	0.54	0.25 to 0.35	0.6 to 0.7	Ca. 80	Ca. 40
Thyroid, Gm.	10.0	7.1 to 8.4	22 to 33	Ca. 35	Ca. 25
Adrenal (one), Gm.	3.5	2.0 to 3.5	5.5 to 6.5	Ca. 60	Ca. 60

* For sources of normal mean figures, see sections *ID* and *F* and figure 9.

anomaly (case 1) may be set apart from the girls and boys who presented the picture of precocious virilization. In that girl (table 6) sexual development had been recorded from its onset at 2½ years to her death at 7¼ years. During that period the sequence of appearance of sexual phenomena was as follows: nipples, breasts, menstruation, pubic hair, axillary hair. This was roughly in conformity with normal adolescent development. The same was true of the speed of her sexual maturation as expressed in terms of number of years covered by the developmental processes. Apart from the scantiness of sexual hair, the degree of

35. Ogston, A.: Ein Beitrag zur Casuistik abnormer geschlechtlicher Entwicklung, Oesterr. Jahrb. f. Paediat. **1**:180, 1872.

maturity attained at the age of 7¼ years (tables 8 and 9; figs. 9 and 10) was estimated to be that of a 14 to 16 year old girl in the stage of unovulatory menstruations or so-called adolescent sterility [36] (no evidence of ovulation or corpus luteum tissue in the maturing ovaries; no excretion of pregnandiol; virginal state of endometrial and vaginal mucosae; mature mammary ducts with small acini). A similar "physiologic" course of precocious maturation was reported in Thoms's patient with cerebellar astrocytoma.[37] However, patients are also on record pre-

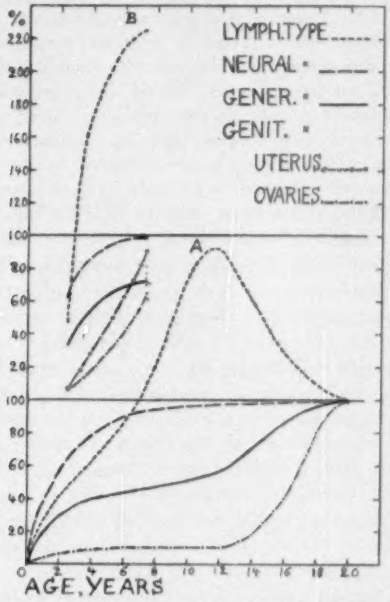

Fig. 9.—Scammon's diagram [22] for growth in weight of four "types of organs," ranging from birth to 20 years of age (abscissa), expressed in per cent of normal adult weight (ordinate). *A* is Scammon's original diagram for normal children. *B* is a diagram for a hyperfeminized girl (case 1). At age of 2½ years, when illness began, Scammon's mean normal data were put in, while figures for patient at 7 3/12 years of age represent actual percentage weights at postmortem study. Stray points for "general type" indicate percentage weights for body as a whole, heart, lungs, liver, pancreas and kidneys.

36. Ashley-Montagu, M. F.: Adolescent Sterility: A Study in the Comparative Physiology of the Infecundity of the Adolescent Organism in Mammals and Man, Springfield, Ill., Charles C Thomas, Publisher, 1946.

37. Thoms and Hershman.[24b] Gesell and others.[25] Greulich, W. W.: Some Observations on the Growth and Development of Adolescent Children, J. Pediat. **19**:302, 1941.

sumably with the "idiopathic" type, in whom complete sexual maturity, with corpus luteum formation and even successful pregnancy, was attained within the incredibly short time of two years (youngest patients, aged 22 months and 5 years, respectively [18]).

In the group of virilized children (tables 6, 7 and 9; fig. 10), the 2 boys (cases 2 and 3), who also belonged to the hypothalamic group of sexual precocity, showed a roughly normal sequence of sexual maturation, too, again with relatively late appearance of pubic and/or axillary hair. The speed of maturation was rapid in one (case 2) and moderate in the other (case 3). Eventual degrees of sexual maturity were estimated in the 2 boys to be sixteen to seventeen years and twelve to fifteen years, respectively. In the remaining 3 children who showed virilization due to the adrenogenital syndrome (cases 4 to 6), the maturational "dissociation" between infantile gonads and precociously virilized penis or clitoris eliminated the testes and ovaries from an estimation of degree of sexual precocity. That degree, when measured by the virility of the penis and the amount of sexual hair present in both sexes, was thought to be between fifteen and sixteen years in all 3 patients.

It has been suggested [38] that in normal adolescents the appearance of axillary hair in boys (*ca.* 15 years of age) indicated a degree of sexual maturity corresponding to that of the menarche in girls (*ca.* 13 years of age) and that both events were closely correlated to certain maturational developments in the skeleton. These were (in girls): 1. In the annual increments in height and weight, there was an accelerating phase three years preceding, and a sharply decelerating phase about three years following, the onset of menstruation. 2. As a rule the first sesamoid bone of the thumb appeared about two years preceding the menarche and was always present at the time of menarche. 3. Fusion of the epiphyses of the terminal phalanges of the fingers, especially of the second finger, coincided within a few months with the menarche. 4. The appearance of the secondary epiphyses to the iliac crests also coincided within a few months with the menarche. Only 2 of the patients (cases 1 and 4) were observed long enough to judge the first of these correlations (figs. 1 and 2). In one (case 1) the menarche occurred at the age of 3 years and as long as four years later there was little indication of even a moderate deceleration of growth. In the other, a boy (case 4), axillary hair was first observed at 5 years; in the two year period preceding this event he had gained about 14 Kg. in weight and

38. Flory.[9c] Shuttleworth.[5e] Shuttleworth, F. K.: Sexual Maturation and the Skeletal Growth of Girls Age Six to Nineteen, Monograph of the Society for Research in Child Development, 1938, vol. 3, no. 5. Simmons, K., and Greulich, W. W.: Menarchial Age and the Height, Weight, and Skeletal Age of Girls Age Seven to Seventeen Years, J. Pediat. **22**:518, 1943. Buehl, C. C., and Pyle, I.: The Use of Age of First Appearance of Three Ossification Centers in Determining the Skeletal Status of Children, ibid. **21**:335, 1942.

TABLE 9.—*Summary of "Biologic Ages," Years and Months, of Six Children with Precocious Sexual Development* *

	Hypothalamic Group									Adrenogenital Group					
	Case 1, Female			Case 2, Male			Case 3, Male			Case 4, Male			Case 5, Female,	Case 6, Female	
Chronologic age, years	5 3/12	6 9/12	7 3/12	7 7/12	8 6/12	8 11/12	2 7/12	3 2/12	4 1/12	3 2/12	5 1/12	7 3/12	7 2/12	4 1/12	9 2/12
Anthropometric Age															
Weight age	11¼	12¾	13	10⅝	13	13	6½	8	9¼	6	12	13¾	10	7	14
Height age	10	11¼	11½	9	10¾	11½	5¼	6	7½	5	9¾	12½	9½	8	12
Somatic age	10½	11	..	..	..	11	..	6½	7 to 9	Ca. 5	Ca. 10	12½	10	6¾	12?
Face height age	5	5	5	..	..	14	..	5 to 6	11	..	..	12	10	..	12?
Skeletal age	10¾	14	15½	12	14 to 15	15 to 16	5¾	6¾	10 to 11	10	13	16	14 to 15	11	18
Dental Age															
Eruption age	5¾	Ca. 7	7¾	..	..	9½	2½+	2½+	2½+	2½+	6¼	8½	8½	..	11½
Roentgenographic age	..	8	8+	..	8	Ca. 10	..	2½ to 3	4	2½	5 to 6	..	7	..	11½
Sexual Age															
Pelvic age	12	13½	14	..	..	12	..	7	9	..	..	15	9½	..	15?
Breast age	12	13	14	(12)	(12)	(13)	3	3	4	3	5	7	7	4	9
Sex hair age	11	12	12	14	15	16	?	12	12+	13	15	16	Ca. 15	11	16
Nongonadal genital age†	15	16	16+	14+	15	16	12+	13	14	14	15+	16	7?	..	9?
Gonadal age	14+	15+	16½	15	15+	16+	12+	14	15	3	5	7	7	..	9
Sex hormone age															
Estrogens	..	3 to 4?	10 to 11?	..	..	..	..	..	..	..	..	..	..	..	..
17-ketosteroids	..	6 to 10	11 to 16	11 to 18	..	11 to 18	5 to 8	5 to 8	..	8 to 12	>Adult	>Adult	>Adult	..	>Adult
Mental age	6¾	6¾	Ca. 7	..	..	7	..	4¾	Ca. 5	3	Ca. 5	Ca. 6½	7¼	3¼	7¾

* This table is based on data presented in tables 1 to 8. Blank spaces mean absence of information; > or + mean more than or over.
† "Nongonadal genitalia" are such structures as penis, prostate, clitoris, vagina and uterus, and in instances marked ? the clitoris was excluded from these structures. See section 16 and figure 10.

17 cm. in height, and in the two year period following it the respective gains were 12 Kg. and 15 cm. The three other skeletal developments listed previously took place in the girl between 6 and 7 years of age, i. e., three to four years following the menarche instead of preceding it or coinciding with it. In the boy (case 4), the appearance of the epiphysis of the iliac crest was timed normally, but both the appearance of the first sesamoid bone of the thumb and the fusion of the terminal phalanges occurred an estimated one to two years after, instead of before or at, the time of axillary hair growth. As for the remaining children, correlations 2 to 4 were unknown in one (case 6) and normal in another (case 5). In one boy (case 3), the first sesamoid bone of the thumb had just appeared at the age of 4 1/12 years, i. e., before any axillary hair was noticed. Such normal correlation had also been found in another boy (case 2) in regard to terminal phalangeal fusion; however, in that boy, the epiphysis of the iliac crest appeared at least half a year earlier than his axillary hair. On the whole, then, the patients' skeletal maturation was at best as far advanced as, but more often less advanced than, their sexual maturation. This also seemed to be the experience of other observers in this field (e. g., Gesell and others [25]).

Precocious sexual development has been artifically produced in immature children by administering chorionic gonadotropin, as well as sex hormones. When the same hormones were given to immature chicks, their gonads and/or secondary sex characteristics, particularly combs and wattles, developed precociously, but body sizes lagged behind that of controls.[39] Similarly, treatment of immature female rats with urine from pregnant animals provoked precocious genital maturation in the presence of "an immature soma"; impregnation by fertile males was delayed until the normal age of fertility of the female rat, suggesting a period of "adolescent sterility." [36]

Urinary excretions of estrogens and 17-ketosteroids have already been discussed in the previous publication (table 2 [1]) and will be commented on later; the patients' "biologic ages" are estimated in table 9. Basal metabolic rates (table 1 [1]) were "normal" for maximum biologic age

39. Kunstadter, R. H.: The Induction of Premature Puberty with Androgenic Substances, Endocrinology **23**:661, 1938. Thompson, W. O., and Heckel, N. J.: Precocious Sexual Development from an Anterior Pituitary-like Principle, J. A. M. A. **110**:1813 (May 28) 1938. Domm, L. V., and Van Dyke, H. B.: Precocious Development of Sexual Characters in the Fowl by Daily Injections of Hebin: I. The Male; II. The Female, Proc. Soc. Exper. Biol. & Med. **30**:349 and 351, 1932. Hamilton, J. B.: Precocious Masculine Behavior Following Administration of Synthetic Male Hormone Substance, Endocrinology **23**:53, 1938. Brenneman, W. R.: Variations in the Reaction of Chicks to Different Methods of Administering Androgens, ibid. **24**:55, 1939. Noble, G. K., and Zitrin, A.: Induction of Mating Behavior in Male and Female Chicks Following Injections of Sex Hormones, ibid. **30**:327, 1942.

in 1 child (case 1) and for chronologic age in 2 children (cases 2 and 6). In the first child (case 1), urinary excretion of creatinine was below normal standards for chronologic age and so it was in an 11 year old girl described by Mattar and his co-workers [24c] (their case 2). Values for urinary creatinine and creatine corresponded to those of normal adolescents in 3 male patients, the present patient (case 2), aged 9, the patient of Mattar and his co-workers (their case 1), aged 11,[41] and Gardiner-Hill and Richardson's patient, aged 8¾.[42] A special creatine excretion test has been devised and tested in two instances of sexual

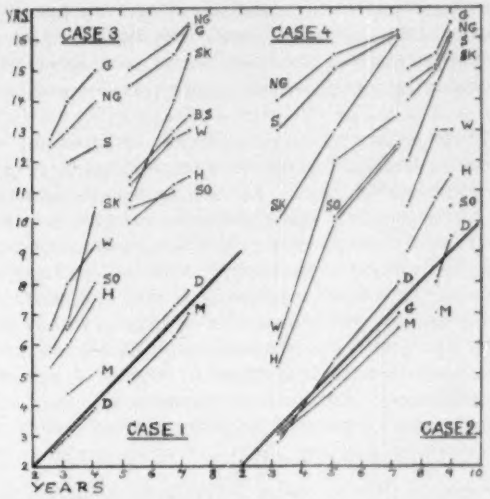

Fig. 10.—Wilkins-Olson-Hughes diagram [23] of biologic growth for cases 3, 1, 4 and 2. Chronologic age in years is on the abscissa, biologic age in years on the ordinate. Heavy diagonal lines represent mean biologic growth of normal children. Lighter dots and lines are to be read case-wise in the vertical direction; they represent the patients' biologic growth. Capital letters indicate biologic ages as follows: *D*, dental age, *M*, mental age, *H*, height age, *W*, weight age, *SO*, somatic age, *SK*, skeletal age, *B*, breast age, *S*, sex-hair age, *NG*, nongonadal genital age and *G*, gonadal age.

precocity.[42] Figures for hemoglobin concentration and red blood cell counts tended to be high in all the present patients and reached adolescent

40. Footnote deleted on proof.

41. Footnote deleted on proof.

42. Gardiner-Hill, H., and Richardson, T. S.: Macrogenitosomia Praecox in One of Twin Boys Without Demonstrable Pathologic Lesion, St. Thomas Hosp. Rep. **4**:35, 1939.

43. Fasold, H.: Ueber den Kreatinstoffwechsel bei Pubertas praecox, Ztschr. f. Kinderh. **51**:527, 1931.

levels in 4 (cases 1, 2, 4 and 6). White blood cell studies were noncontributory. The lymphoid system was hyperplastic in the preadolescent fashion in 1 girl (case 1, table 8; fig. 9).

In regard to mental maturation, the majority of the patients had low normal to normal intelligence for their chronologic age, with ranges for intelligence quotients from 80 to 102 and for mental ages of 3 to 7¼ years (table 9). Their socioeconomic background varied from poor to lower middle class. The only child in our series with a superior intelligence (intelligence quotient of 155) was the son of well-to-do, cultured persons. However, it was felt that neither this boy nor the other 5 patients in this series showed the slightest advance in personality development over what was normal for their chronologic age. In particular, there was no trace of adolescent behavior, of precocious interest in the opposite sex or of outright sexual aggressiveness in any one of these children.

The literature on the subject is largely in agreement with these observations. Although a certain unevenness in the maturation of various areas of mind and personality was noticed by some observers,[44] the majority have stressed the lack of precocity, and even the prevalence of some retardation, in the neuromental development of these patients.[45] This was also the result of the elaborate study of Gesell and his associates [25] in which they tested a patient in six different psychologic areas between the ages of 4 and 17 years. Of 80 children with pubertas praecox,[46c] only 3 girls and 3 boys showed overt sexual behavior of adolescent character. The rare instances of precocious propagation in boys give confirmatory evidence.[46] Mental infantilism was also maintained in artificially induced sexual precocity of childhood.[39] On the other hand, hormonal treatment of immature chicks and rats [47] resulted in precocious

44. Bormann, E.: Pubertas praecox und psychische Reifungsverhältnisse, Arch. f. Psychiat. **111**:666, 1940. Bürger-Prinz, H.: Ein Fall von Pubertas praecox, Nervenarzt **15**:438, 1942.

45. (*a*) Leiner, T. H.: Pubertas Praecox with Special Attention to Mentality, Endocrinology **4**:369, 1920. (*b*) Dennis, W.: Effect of Pubertas Praecox on Age at Which Onset of Walking Occurs, Am. J. Dis. Child. **61**:951 (May) 1941. (*c*) Keene, C. M., and Stone, C. P.: Mental Status as Related to Puberty Praecox, Psychol. Bull. **34**:123, 1937.

46. Stone, R. K.: Extraordinary Precocity of the Development of the Male Sexual Organs and Muscular System in a Child Four Years Old, Am. J. M. Sc. **24**:561, 1852. Rolleston, H. D.: The Endocrine Organs in Health and Disease, London, Oxford University Press, 1936.

47. Footnote 39. Mirskaia, L., and Crew, F. A. E.: Maturity in the Female Rat, Proc. Roy. Soc. Edinburgh **50**:179, 1930; On Genital Maturity in an Immature Soma, J. Exper. Biol. **7**:248, 1930. Stone, C. P.: Precocious Copulatory Activity Induced in Male Rats by Subcutaneous Injections of Testosterone Propionate, Endocrinology **26**:511, 1940. Beach, F. A.: Analysis of Factors Involved in the Arousal, Maintenance and Manifestations of Sexual Excitement in Male Animals, Psychosom. Med. **4**:173, 1942.

sexual behavior, such as crowing, wing flapping and treading in the chicks and copulatory movements in the rats. The greater frequency of this effect in immature animals might be the result of the shortness of their period of "neutral childhood."[48]

III. COMMENT

Two questions related to the problem of hormonal stimuli versus tissue response in the developmental pattern of these sexually precocious children present themselves for brief comment (table 9; fig. 10).

A. How did one and the same tissue of different patients at comparable ages respond to different blood levels of a given hormone?

The hormones suitable for testing this point in the present series were the androgenic hormones, expressed in terms of daily urinary 17-ketosteroid excretions. These were moderately increased for age in the hypothalamic group of patients, cases 1 to 3 (2 to 11.5 mg. per day), and excessively increased in the adrenogenital group, cases 4 to 6 (25 to 53 mg. per day; 5 mg. in case 4 at the age of 3 2/12 years). At comparable ages, the higher androgen levels in the latter group caused a greater stimulation of skeletal maturation, and in the boys of penile growth, than did the lower androgen levels in the former group (for skeletal maturation compare cases 3 and 4 at 3 years, cases 1 and 4 at 5 years, cases 2 and 6 at 9 years; for size of the penis, cases 3 and 4 at 3 years, table 7). In some instances no difference in skeletal age was noted, however. Biologic ages for weight, height and other linear dimensions failed to show significant differences in tissue response between the two groups of patients. This lack of difference of androgenic response in the area of "general" growth may be due to the fact that in the hypothalamic group the relatively low androgen levels were compensated for by an overproduction of growth hormone which was not present in the adrenogenital group with their high androgen levels.

B. How did different tissues of one and the same patient at a given age respond to the given stimulus of one or more hormones? This point will be dealt with in two sections, one having to do with tissues that did more or less respond to hormonal stimuli and the other with tissues that responded little or not at all.

1. Among the tissues more or less responsive in the hypothalamic group to the stimulation of growth hormone, gonadotropins and androgens or estrogens and, in the adrenogenital group to the stimulation of the androgens, the following order of decreasing responsiveness was established: gonads (in the hypothalamic group only), nongonadal primary genitalia, secondary sex characteristics, skeletal epiphyses,[49]

48. The latter two reversed in cases 1 and 6.

body and organ masses and metaphyses of long bones. The advancement of sexual over skeletal maturation was the more spectacular the younger the children were.

2. Two tissues responded, peculiarly, little or not at all to the "hormonal crisis" of sexual precocity, namely, the teeth and the central nervous system. The reactions of these organs may be referred to as the "two major disharmonies" in the otherwise fairly harmonious pattern of precocious sexual maturation.

As for the teeth, their slow response to the hormonal stimulation of sexual precocity should not be too surprising in view of what happens to them during normal development. The following passage is worth quoting [48]:

> Quite obviously, the underlying factors which condition the development of teeth are radically different from those determining all the other measurements which have been considered. . . . The writer suspects that the explanation is to be found in the fact that the most intensive development of teeth occurs prior to the onset of the endocrine stimulation which, by hypothesis, is responsible for the timing of the menarche and of patterns of growth in all other available measurements. The period of most active eruption of permanent teeth is from age 9.5 to 10.5, whereas the period of most active growth in other available measurements occurs approximately two years later.

The face and jaws also failed to respond hormonally in the hyperfeminized girl (case 1) whose androgenic stimulation probably was overcompensated by hyperestrinism. On the other hand, in the 5 children with precocious virilism, the face and jaws did react to excess androgens according to general somatic patterns. The number and scope of these observations are, however, still too small to permit final conclusions.

The endocrine stimulation of sexual precocity produced even less response in the maturation of the brain than in that of the teeth. In case 1, it is true, the brain weighed 100 Gm. above the expected weight, and skulls were large in cases 2 and 3. However, intellectual and emotional behavior in the 6 patients, as well as in the majority of instances recorded in the literature, were on, or below, the normal level for chronologic age. Only a few of those children attained psychosexual maturity. Such maturity, then, would seem to be largely independent of, though in normal adolescents coincidental with, hormonal maturation.[49] Its appearance would rather seem to be controlled by the autonomous laws which govern the normal development of the brain apart from the area of the hypothalamus responsible for the release of hormones of the anterior lobe of the pituitary gland.

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49. Bruch, H.: Puberty and Adolescence: Psychologic Considerations, in Advances in Pediatrics, New York, Interscience Publishers, Inc., 1948, vol. 3, p. 218.

This "amazing degree of invulnerability . . . [and] of preferential immunity . . . to certain forms of endrocine imbalance" [25] that the central nervous system shares with the teeth has been the subject of much speculation. Some writers have pointed out the common ectodermal anlage of the two structures. However, on the one hand, ectodermal structures other than the brain and the dental crowns, such as the epidermis and its appendages, are usually perfect reactors to all sorts of endocrine stimuli including the sex hormones. On the other hand, the roots of the teeth are of mesodermal anlage like bones in general and yet react poorly to the same stimuli. There seems to be at present no satisfactory solution of the problem.

For the purpose of describing processes of differential growth, Needham [50] introduced a useful terminology. He defined "heterauxesis" as "the relation of the growth rate of a part of the developing organism (whether morphological or chemical) to the growth rate of the whole." Scammon's graph (fig. 9*A*) was a method of visual representation of such a heterauxetic system, relating the growth rate of normal children's lymphoid, neural and genital types of organs to that of their general type of organs and the body as a whole. In regard to these relationships, Needham posed the problem "whether, if growth were greatly retarded or accelerated, heterauxesis would follow suit. . . . Further investigations on the temporal deformability of heterauxetic relations would be of interest." Concerning greatly accelerated growth, a partial answer might be given on the basis of the present studies of sexually precocious children. As is seen in fig. 9*B*, heterauxetic relations between Scammon's four types of rates for organ growth did roughly follow suit under conditions of acceleration of growth in case 1. Figure 10 shows that heterauxesis, also roughly, followed the normal pattern in all the patients when maturational rates for body weight, body height, other somatic dimensions, skeletal calcifications, secondary sex characteristics and nongonadal primary genitalia were considered.[51] Regarding the gonads, rough conformity with normal heterauxesis, morphologic and chemical, was observed in the hypothalamic group of patients. On the other hand, there was nonconformity in the adrenogenital group, earlier referred to as "dissociated virilization." Nonconformity with normal heterauxesis was also observed in both groups of patients with regard to dental and mental growth rates. These temporary deformities of heterauxetic relationships had previously been called the "two major disharmonies" in the pattern of precocious sexual development.

50. Needham, J.: Biochemistry and Morphogenesis, London, Cambridge University Press, 1942; especially pp. 531, 559 and 684.

51. In the latter two areas some obvious exceptions were to be made for the virilized girls.

IV. SUMMARY AND CONCLUSIONS

In 6 children with precocious sexual development described in an earlier publication, extensive studies in growth and maturation were made. The purpose of these investigations was to evaluate degrees of maturational changes in terms of a variety of "biologic ages."

The studies consisted of complete somatic and cephalofacial measurements, dental examinations, skeletal and dental roentgenograms, description of sex characteristics, determinations of sex hormones and psychometric tests. Investigative technics and mean normal standards for age are presented in section I, as well as by way of tables and graphs.

In all the patients, regardless of the hypothalamic or adrenocortical origin of their condition, a roughly proportionate macrosomia was observed. This included sizes of organs at postmortem examination in one of the children.

The growth spurt that occurred during the early years of illness began to level off at 7 to 9 years of age, when the children approached early adolescent norms for size which coincided with a more or less advanced fusion of the epiphysial lines of the long bones. At that age, body proportions as judged by transverse measurements of shoulders and pelvic girdles were definitely those of normal adolescents.

Skull size and development of paranasal sinuses were not at all uniform and could not be used for an evaluation of biologic maturation.

The degree of skeletal development was spectacular in all patients, regardless of the cause of their sexual precocity. At any time of their illness, their skeletons, biologically speaking, were about twice or three times as "old" as was to be expected chronologically. As a rule, degrees of skeletal maturation lagged behind degrees of sexual maturation, and mean normal age correlations between critical stages in the two systems were usually disturbed in favor of the latter.

Most accelerated of all bodily systems in anatomic, as well as functional development, were part or all of the primary genitalia and secondary sex characteristics. Sequence, speed and degree of sexual maturation roughly corresponded to those seen at various stages of normal adolescence. More or less advanced maturation of the testes or ovaries was seen only in the hypothalamic group of patients. In the adrenogenital group, regardless of sex, the gonads remained infantile and, thus, were maturationally "dissociated" from the rest of the children's virilized bodies.

In the case of the androgenic hormones, there was a certain correlation between tissue responses in different patients and their levels of urinary hormone excretion. The order of degrees in which different tissues of the same patient responded to given hormone levels at a given age was also established.

Least advanced in maturation of all bodily systems, if advanced at all, were the teeth and the central nervous system. Dental age was normal for chronologic age or, at the most, one to two years advanced in all patients of this series. Facial growth, including growth of the jaws, appeared to be on the same infantile level in the case of the hyperfeminized girl. However, in all the virilized patients face and jaws seemed to have outgrown dentures to a greater or lesser degree.

Mental age was on or near the level of chronologic age in all the patients, intellectual performances ranging from about 85 to 150 per cent of normal. Personality development, including psychosexual maturation, was decidedly childlike throughout the series. A few patients who showed overt sexual behavior were recorded in the literature.

The unusual responses of these two tissues, dental and nervous, to the "endocrine crisis" of sexual precocity were referred to as the "two major disharmonies" in the clinical picture under discussion. In Needham's terminology, they were also described as temporary deformities of the heterauxetic relationships in the growth pattern of the child.

The causes for the singular unresponsiveness of the teeth and brain in sexually precocious children remain undetermined. Gesell and his associates [23] wrote: "There are deeply entrenched mechanisms of maturation which tend to preserve the integrity of the nervous system. . . ." The teeth, in the majority of instances, will have to be included in this statement.

Dr. W. M. Krogman and Dr. R. M. Snodgrasse, Department of Anthropology, University of Chicago, (now at the Graduate School of Medicine, University of Pennsylvania, Philadelphia), Dr. Allan T. Kenyon and Dr. Richard L. Landau, Department of Medicine, Dr. Earl P. Benditt, Department of Pathology, Dr. James R. Blayney, Dr. Jack L. Craig and Dr. E. Bushra, Zoller Dental Clinic, and Anna S. Elonen, Ph.D., Department of Psychology, Division of Psychiatry, cooperated in these studies.

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FLUOROACETATE POISONING

A Review and Report of a Case

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DURING the war years intensive investigations were conducted in this country with the object of discovering a more effective rodenticide than had previously been available. As a result of these studies, sodium fluoroacetate (CH_2FCOON_a) was introduced as a rodenticide and reported on by Kalmbach.[1] During this early period of investigation the laboratory number "1080" was used to represent the compound. Since then, this number has been retained and sodium fluoroacetate is often referred to by this numerical designation alone in the literature on rat extermination.[2]

This compound has gained attention recently not only because of its economic and military importance as a potent rodenticide but also because its numerous important pharmacologic properties have engaged the interest of physiologists, biochemists and neurologists, as well as pharmacologists and toxicologists.

Sodium fluoroacetate lacks one of the properties desirable in an ideal rodenticide, i. e., innocuousness for man and domestic animals. It is a potent poison for all mammals, including man, and experimental study indicates it is one of the most poisonous substances known.

Much study has been devoted to the experimental poisoning of laboratory animals with 1080, but to our knowledge no case of human poisoning by fluoroacetate has been reported. Since the introduction of

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1. Kalmbach, E. R.: "Ten-Eighty," War-Produced Rodenticide, Science **102**:232, 1945.

2. (*a*) Ormsbee, R. A.: A Summary of Field Reports on 1080 (Sodium Fluoroacetate), Report no. 163, National Research Council, Insect Control Committee, Dec. 17, 1945; (*b*) Instructions for Using Compound 1080 (Sodium Fluoroacetate) as a Rodent Poison, ibid., July 1946. (*c*) Philips, F. S.: Symposium on Advances in Pharmacology Resulting from War Research: Insecticides and

1080 as a rodenticide, cases of human poisoning have been expected. Toxicologic studies in mammals, including monkeys, were conducted, and a search for an antidote was made.[2]

Marais [4] reported that monofluoroacetic acid is the toxic principle of Dichapetalum cymosum, a toxic plant which the South African farmers call "gifblaar." He found that 1.0 to 1.5 Gm. per kilogram of body weight orally of the dried plant is a lethal dose for rabbits.

The present paper reports a case of fluoroacetate poisoning in man, together with a brief review of experimental work on fluoroacetate toxicity which may have a bearing on the medical care of subsequent cases of human poisoning by this agent.

REPORT OF CASE

N. D., a 2 year old Negro boy, was admitted to the pediatric receiving ward of the Cincinnati General Hospital, apparently moribund, about six hours after he had licked the screw top of a bottle of rat poison. There were a few crystals left from the evaporation of the clear, colorless poison solution on the bottle top which the child had removed while playing. The parents did not know whether the child had drunk any of the solution, but they had found him licking the crystals from the stopper.

Rodenticides, Federation Proc. **5**:292, 1946. (*d*) Hughes, J. H.: Studies in Deratization of Surface Vessels by Means of 1080 (Sodium Fluoroacetate), Pub. Health Rep. **62**:933, 1947. (*e*) DuBois, K. P.: New Rodenticidal Compounds, J. Am. Pharm. A. (Scient. Ed.) **37**:307, 1948. (*f*) Gratch, I.; Purlia, P. L., and Martin, M. L.: Effect of Sodium Fluoroacetate (1080) in Poisoned Rats on Plague Diagnosis Procedures: Preliminary Reports, Pub. Health Rep. **64**:339, 1949.

3. (*a*) Chenoweth, M. B., and Gilman, A.: Studies on the Pharmacology of Fluoroacetate: I. Species Response to Fluoroacetate, J. Pharmacol. & Exper. Therap. **87**:90, 1946; (*b*) II. Action on Heart, Bull. U. S. Army M. Depart. **7**:687, 1947. (*c*) Chenoweth, M. B.: Pharmacology of Fluoroacetate, Federation Proc. **5**:171, 1946. (*d*) Chenoweth, M. B., and St. John, E. F.: Studies on the Pharmacology of Fluoroacetate: III. Effects on the Central Nervous System of Dogs and Rabbits, J. Pharmacol. & Exper. Therap. **90**:76, 1947; (*e*) Spike and Dome Formation Produced in Dog's Encephalograms by Fluoroacetic Acid, A. Research Nerv. & Ment. Dis., Proc. **26**:299, 1947. (*f*) Foss, G. I.: The Toxicology and Pharmacology of Methyl Fluoroacetate (MFA) in Animals, with Some Notes on Experimental Therapy, Brit. J. Pharmacol. **3**:118, 1948. (*g*) Ward, A. A., Jr.: Convulsive Activity Induced by Fluoroacetate, J. Neurophysiol. **10**:105, 1947. (*h*) Quin, J. I., and Clark, R.: Studies on the Action of Potassium Monofluoroacetate (CH_2FCOOK) [Dichapetalum Chymosum (Hook) Engl.] Toxin on Animals, Onderstepoort J. Vet. Sc. **22**:77, 1947. (*i*) Williams, A. T.: Sodium Fluoroacetate Poisoning, Hosp. Corps Quart. **21**:16, 1948. (*j*) Possible Treatment of Sodium Monofluoroacetate (1080) Poisoning, Surgeon Circular M. Sect. Far East Command **4**:9, 1949.

4. Marais, J. S. C.: Monofluoroacetic Acid, the Toxic Principle of "Cifblaar," Dichapetalum cymosum (Hook) Engl., Onderstepoort J. Vet. Sc. **20**:67, 1944; Chem. Abstr. **39**:4116, 1945.

Almost immediately after licking the screw top, the boy vomited, and he continued thereafter to vomit and retch frequently. Three hours after the ingestion a local physician was consulted because of persistent nausea and emesis. He prescribed a cathartic of unknown nature which the child vomited soon after administration. Vomiting and retching persisted; the child could retain no food or fluids, and about six hours after ingestion of the poison he began to have generalized convulsive movements and became stuporous. He was then immediately brought to the hospital.

The bottle of rat poison, brought by the parents to the hospital, contained several hundred cubic centimeters of a clear, colorless solution. The bottle was two-thirds full, and it was labeled in a handwritten script, "Rat Poison—1080." The nature of the poison was unknown to the parents, who had purchased it from a passing peddler two years previously.

Past History.—N. D. had previously been a healthy child. He had had a normal, full term, spontaneous delivery and an uneventful neonatal period. He had had no contagious diseases other than common colds. He had never had convulsions or any other neurologic disorder.

Emergency Therapy.—On his admission to the receiving ward, the child was in critical condition. Because of his critical state, only a cursory physical examination on admission could be done. He was in tetany, comatose and exhibiting carpopedal spasm and tetanic convulsive movements, irregular respirations and great cardiac irregularity. As an emergency measure, 0.5 Gm. of 5 per cent solution of calcium gluconate U. S. P. was given intravenously, and a continuous intravenous infusion was started with 150 cc. of isotonic sodium chloride solution U. S. P. During the administration of the calcium gluconate there were a few seconds of cardiac asystole, and thereafter the previous irregular cardiac rhythm was resumed, but at a much slower rate. The tetanic convulsive movements stopped immediately on the intravenous administration of the calcium gluconate, and the child became completely flaccid. About one-half hour later 120 cc. of milk containing 3 Gm. of added calcium chloride U. S. P. was administered by gavage, but shortly thereafter the boy vomited 80 cc. of this. Only at this time was it possible to make a more thorough physical examination.

Results of Physical Examination.—His temperature was 97.4 F. (rectum); the pulse rate was irregular, 40 to 50 per minute, and respirations were 26 per minute.

The boy was a well developed and well nourished Negro child in deep stupor, completely flaccid, with no muscle spasm. Convulsive movements had stopped. The skin was clear, and no lymphadenopathy was present. The eyes were deviated upward and to the right. The pupils were round and equal and reacted normally to light. Cardiac action was irregular and slow, and there was a soft apical systolic murmur. Blood pressure in the right arm with the child recumbent was 94 systolic and 70 diastolic (with a 2 inch [5 cm.] cuff). Respirations were shallow and somewhat irregular. The lungs were clear to percussion and auscultation. There was now no carpopedal spasm, and no Chvostek sign could be elicited. Deep reflexes were hypoactive, and the Babinski response was positive.

Therapy and Course.—The 150 cc. of isotonic sodium chloride solution was followed by administration of 2 Gm. of calcium gluconate in 700 cc. of 5 per cent dextrose solution by slow intravenous drip during the next twelve hours. A few hours after his admission the child became responsive and appeared to recognize his father. He continued to vomit most of the milk given in the receiving ward by gavage. Four hours after his admission a generalized tonic-clonic convulsion lasting several minutes occurred and was followed by deep postconvulsive coma from which

the patient could not be aroused. One hour later he became slightly responsive again, grunted and appeared to recognize his father but could not speak or sit up. After one hour he again had a generalized tonic-clonic convulsion and thereafter remained comatose during the entire night.

The nature of the rat poison the child had ingested was unknown. Since there was still the possibility that the poison contained arsenic, BAL (2,3-dimercaptopropanol) was administered intramuscularly at four hour intervals, 3 mg. per kilogram of body weight—the child's weight was estimated at 10 Kg.—for a total of five doses. Its use was then discontinued because analyses failed to reveal any arsenic or heavy metals in the rat poison.

Because it was strongly suspected from his gastric symptoms and tetany on his admission that the patient had fluoride poisoning, 1 Gm. more of calcium gluconate was administered through the constant intravenous drip, and thereafter no further calcium therapy was given.

On the day following his admission the child was limp and unresponsive. Breathing was regular. The gag reflex was present; deep tendon reflexes were active and equal. There was no stiffness of the neck. At frequent intervals, however, tonic convulsions occurred, during which the child occasionally groaned. At times spasticity persisted for several minutes, remaining longer on one side than on the other. His eyes wandered about; the pupils remained round, regular, equal and reactive to light. The child did not respond to painful stimuli until they were of severe intensity and then only groaned, showing no withdrawal response. The heart rate was 96 per minute. Cardiac rhythm remained irregular, with exaggerated sinus arrhythmia and many dropped beats, occasional periods of asystole or of complete arrhythmia (fibrillation) and infrequent runs of what appeared to be paroxysmal tachycardia. Intervals of normal rhythm occurred. Atropine U. S. P. was administered intramuscularly in a dose of 0.125 mg. which was repeated in fifteen minutes, twenty-one hours after his admission; this therapy was followed by a period of regular cardiac rhythm, with a pulse rate of 180 per minute.

The cardiac rhythm and the quality of cardiac sounds continued to change frequently during the first three days in the hospital. Tonic convulsions lasting several minutes occurred many times every hour—sometimes about every ten minutes for many successive hours. During the tonic convulsive spasms the pupils dilated and remained inactive to light. Between seizures the pupils were miotic and responsive to light. No carpopedal spasm or Chvostek sign could be demonstrated.

On the third day in the hospital the tonic convulsions gradually subsided, but the child remained comatose. Respirations were regular and shallow, but no cyanosis was present. The pulse became regular, with periods of pronounced sinus arrhythmia. In the afternoon the boy suddenly had a long period of apnea while a new constant intravenous infusion was being started. Artificial respiration was performed for three minutes, with an oxygen mask over the child's face, before his breathing was again resumed spontaneously. Later that day a second period of apnea occurred, during which artificial respiration was again required. In the interval respiration had become regular. A mechanical respirator was kept in readiness in the event of a third such episode, but its use was not required. In the evening the boy was noted to whimper on painful stimulus and to be slightly more responsive than previously.

On the fourth day the child remained unresponsive, with shallow, slow respirations (14 per minute). Administration of amobarbital (amytal®) had been stopped.

There was no cyanosis. His eyes wandered less but became divergent, and his pulse was full, with decided sinus arrhythmia. He lay stuporous and totally flaccid. No further tonic convulsions occurred.

In the evening of the fourth day—one hundred hours after ingestion of the poison—the child began to open his eyes and look about. He tried to talk but was unable to articulate. He could neither sit up nor reach for objects but appeared quite alert. During the course of a few hours a remarkable change in consciousness and responsiveness occurred. On the fifth and sixth days he rapidly regained all his motor ability, slowly lost his drowsiness and became articulate. On the evening of the sixth day he was clinically well. He was able to sit up and to play, and, according to his father, he could speak and perform as well as he could before his illness.

The constant intravenous infusion was continued until the morning of the fifth day, when the boy was finally taking fluids orally. Total fluid intake intravenously on the second, third, fourth and fifth days was 850, 1,450, 2,100 and 1,700 cc., given as 5 per cent dextrose solution except that 100, 200, 300 and 200 cc. of isotonic sodium chloride solution was administered on each of the successive days.

The boy was discharged well from the hospital on the eleventh day.

Laboratory Data.—Electrocardiograms were taken on the second, third, fourth and seventh days, but none were recorded during the periods of most serious arrhythmia. They revealed in all tracings a pronounced sinus arrhythmia. The P-R interval was 0.10 second and the QRS complex was 0.06 to 0.07 second, with the rate varying between 90 and 130 per minute on the respective recordings. One record revealed many premature ventricular contractions. On the third day, prominent T waves in leads I, II and IV were noted, with a Q-T interval of 0.34 second, and the S-T segment was elevated in all leads. On his discharge the electrocardiogram was normal.

During the hospitalization, results of four hemoglobin determinations ranged between 11.0 and 11.2 Gm. per hundred cubic centimeters and red blood cell counts between 4,000,000 and 4,300,000. The white blood cell count on his admission was 9,900, with 71 per cent neutrophils, 26 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophils. During the remainder of the course in the hospital, the white blood cell count ranged between 7,100 and 8,900, with 61 to 65 per cent neutrophils. Four uninalyses gave normal results, with no cells, casts or albumin, acetone or sugar present. On the third day serum chemical values were: 91.2 milliequivalents of chloride per liter, 6.4 mg. of phosphorus, 25 mg. of nonprotein nitrogen and 6 Gm. of total protein, per hundred cubic centimeters. Alkaline phosphatase measured 8.4 Bodansky units. On the fourth day, blood urea nitrogen was 21.1 Gm. per hundred cubic centimeters and chloride was 92.2 milliequivalents per liter.

Roentgenograms of the chest, skull and long bones all showed a normal appearance on the day before his discharge from the hospital, and teleroentgenograms of the chest revealed a normal cardiac shadow.

Lumbar puncture was performed on the second day, and an initial pressure of 170 mm. of water was noted. Dynamic pressure was normal, and 10 cc. of clear, colorless cerebrospinal fluid was removed. A cell count on this fluid revealed no red blood cells and 6 white blood cells per cubic centimeter, all lymphocytes. The Wassermann reaction of the fluid was negative. There were 28.8 mg. of protein and 111 mg. of sugar per hundred cubic centimeters and 118.6 milliequivalents of chloride per liter.

The bottle of rat poison was brought to Dr. Francis F. Heyroth, of the Kettering Laboratory of Applied Physiology of the College of Medicine of the

University of Cincinnati, for analysis. Analysis was performed to ascertain what poisons were in the "Rat Poison—1080," since it may well have been a crudely compounded mixture instead of pure 1080, as the label implied. No heavy metals or arsenic was found. Analysis for total fluorine revealed 1.35 Gm. per liter (0.135 per cent fluorine). Decomposition (at a temperature somewhat above 300 F.) of the residue on evaporation of the solution indicated the probable presence of an organic compound. Sodium fluoride would not melt with decomposition. Steam distillation of the acidified solution yielded some fluorine-containing material in the distillate.

Two twenty-four hour specimens of urine collected on the third and fourth (1,500 cc.) and fourth and fifth (450 cc.) days of the child's illness were analyzed for fluorine content: 0.32 and 0.63 mg. of fluorine per liter, respectively, was found, and these values were within the limits of normal controls. However, the toxicity of sodium fluoroacetate is so great that it is unlikely that a case of poisoning by 1080 could be proved or disproved by analysis of the urine.

Follow-Up Observations.—One year after his discharge from the hospital, the boy, now 3 years old, appeared normal and healthy. Mental and physical development had proceeded normally, and there had been no further convulsions or other symptoms of neurologic disorder. Results of physical examination were within normal limits, with a pulse rate of 120 and prominent sinus rhythm; the size and shape of the heart were normal to percussion. Blood pressure was 94 systolic and 60 diastolic. Cardiac sounds were of good quality, and no murmurs were present. Neurologic examination gave entirely normal results.

Follow-up laboratory studies revealed a hemoglobin concentration of 11.5 Gm. per hundred cubic centimeters. White blood cells numbered 7,700, with 24 per cent neutrophils and 76 per cent lymphocytes. Basal urea nitrogen was 9.7 mg. per hundred cubic centimeters. Urinalysis showed nothing abnormal. The Wassermann reaction was negative. The electrocardiogram revealed a rate of 115 per minute, a P-R interval of 0.12 second and a Q-T interval of 0.32 second, with sinus arrhythmia, sinus tachycardia and occasional premature ventricular contractions.

COMMENT

The circumstances surrounding the present case are confusing. Two years before the poisoning, the patient's parents had bought from a neighborhood peddler an old pint (473 cc.) whisky bottle filled with a clear solution, clearly labeled in freehand script, "Rat Poison—1080." The poison had been employed with success against rats near the home, but the bottle—still two-thirds full—had been left in a cupboard. Not until Dr. Francis F. Heyroth identified the label as referring to sodium fluoroacetate were we familiar with the nature of the poison in the flask. Subsequent study at the Kettering Laboratory proved the solution to contain fluorine in a concentration of 0.135 per cent, with no arsenic or heavy metals present. The fluorine was present largely in the bound, organic form, but some inorganic fluorine was also detected. This is not surprising, for in the preparation of sodium fluoroacetate contamination with fluoride ions occurs unless special precautions are taken. For this reason careful pharmacologic studies of experimental poisoning have usually been performed with methyl

fluoroacetate, but the toxicity of both sodium fluoroacetate and methyl fluoroacetate is dependent on the fluoroacetate part of the molecule and on equimolar dosage is identical. Fluoroethanol [2a] and fluoroacetphenylhydrazide (fanyline)[5] have also been studied, and their toxicity is found to depend on the fluoroacetate which is produced in the body from these compounds. The present patient was known only to have licked crystals of fluoroacetate from the screw top of the bottle, and, if he had drunk any liquid, he could not have taken more than a few cubic centimeters. From the analysis of total fluorine, the pint bottle could contain only about 1.5 Gm. of sodium fluoride (3 mg. per cubic centimeter), if all the fluorine were present in the form of the fluoride ion. There is no possibility that the child could have obtained more than a few milligrams of sodium fluoride per kilogram of body weight, and this would have been too small a dose to account for his illness. If the fluorine were all present as 1080, there would have been 7.11 Gm. of the poison per liter, or 7.11 mg. per cubic centimeter. Ingestion of the crystals from the evaporation of a few cubic centimeters of such a solution or of a few cubic centimeters of the solution itself could well account for the child's illness. He undoubtedly obtained relatively pure sodium fluoroacetate with little contaminating ionic fluoride. He could easily have obtained many milligrams of the 1080, but the exact dose he received is unknown. Thus, although complete isolation and characterization of the material in the flask of "Rat Poison—1080" are not available, circumstantial evidence points strongly to the fact that we are here dealing with a case of pure sodium fluoroacetate poisoning.

The clinical picture closely paralleled that seen in experimental poisoning in laboratory animals, and the total recovery without sequelae is what would be expected from observations of those few animals which have survived poisoning severe enough to produce signs and symptoms.

EXPERIMENTAL TOXICOLOGIC STUDIES

Chenoweth and Gilman [3a-c] and Chenoweth and St. John [3d,e] extensively studied the pharmacologic aspects of fluoroacetate. They investigated its effects on 11 species of mammals, on chickens and on frogs. They reported no pharmacologic similarity between the action of fluoroacetate and that of other monohalogen derivatives of acetic acid. Poisoning with this compound is totally different from that produced by the fluoride ion. In fluoroacetate the fluorine is tightly bound in a fluorine-carbon linkage which can be split only by harsh treatment, such as pyrolysis in a free flame or exposure to hot sulfuric acid with potassium

5. Karel, L.: The Rodenticide Activity of Fluoroacetphenylhydrazide ("Fanyline") and Its Oral Toxicity to Several Species, J. Pharmacol. & Exper. Therap. 93:287 (July) 1948.

dichromate. These authors divided the mammalian species studied into four groups, this classification depending on the nature of the response to the poison: group I (rabbit, goat, horse, spider monkey): no central nervous system action observed, death being always due to cardiac effects with ventricular fibrillation; group II (cat, pig, rhesus monkey): both cardiac response and central nervous system affected, death usually resulting from respiratory failure during convulsions, but occasionally from ventricular fibrillation; group III (dog, guinea pig): epileptiform convulsions, with death due to cessation of respiratory activity; central nervous system primarily affected and no cardiac abnormalities observed; group IV (rat, hamster): atypical response with respiratory depression and delayed bradycardia; ventricular fibrillation rare.

Chickens exhibited both central nervous system and cardiac effects and frogs only central nervous system effects, with convulsions followed by flaccid paralysis and, in those which survived, complete recovery.

The lethal dose for 50 per cent of the various animals (LD_{50}) in milligrams per kilogram of body weight was quite different: dog 0.06, rabbit 0.2 to 0.25, guinea pig 0.35, pig 0.4, cat 0.5, goat 0.5, horse 0.5 to 1.75, hamster 2.5 to 5.0, rhesus monkey (Macaca mulatta) 4.0, rat 5.0, spider monkey (Ateles geoffroyi) 14.0, chicken 15 and frog 300. LD_{50} for man has been estimated at 5 mg. per kilogram of body weight.

In these studies the route of administration was found to be unimportant, the lethal doses being the same for all routes. Latent periods before the appearance of symptoms after intravenous injection of methyl fluoroacetate of one to two hours were always observed, and even with huge doses these latent periods did not disappear.

The rhesus monkey was carefully studied, and poisoning in this species was treated by various means in an attempt to find an antidote. One hour after injection of 10 mg. per kilogram of body weight of methyl fluoroacetate, Chenoweth and Gilman observed occasional premature ventricular contractions; two hours after injection T waves in the electrocardiogram were accentuated, and a few minutes later convulsions, heralded by blinking, nystagmus, twitching of facial muscles, defecation and some salivation, occurred. After the jerking, symmetric tonic convulsion, the animals remained conscious for a short while and persistent changes in the T waves of the electrocardiogram and alterations in the pulse rate and heart sounds were noted. A second convulsion occasionally occurred. Four hours after injection, pronounced alteration in T waves in the electrocardiogram and a 50 per cent pulse deficit were present, and one-half hour later ventricular fibrillation occurred. Quinidine, papaverine and sodium para-aminobenzoate were used as possible antidotes for ventricular fibrillation without effect. The only effective therapy was intracardiac administration of procaine hydrochloride and cardiac massage, which in many instances produced

reversal of an episode of ventricular fibrillation to a normal contraction, but in only 2 cases were animals permanently saved by this method, since recurrent attacks of fibrillation eventually became irreversible.

Fluoroacetate poisoning was studied in the cat by Chenoweth and his associates[8a-e] and by Ward.[8g] After 0.5 to 2.0 mg. per kilogram of body weight of fluoroacetate was given intravenously, the symptoms, after a latent period of one hour, were ushered in with sudden retching and vomiting, salivation, pupillary dilatation, micturition, hyperpnea, hyperexcitability and a myotonic convulsive state, with flexion of the forelegs in a posture resembling carpopedal spasm. Occasional violent myoclonic convulsions developed, with intervening periods of flaccidity, and their frequency increased from about one every ten minutes until a status epilepticus without flaccidity prevailed. Death was usually caused by depression of the respiratory center. In a few cases animals were tided over an apneic period with artificial respiration.

In the rhesus monkey convulsions were ablated or averted by sedative doses of pentobarbital sodium U. S. P. (15 to 20 mg. per kilogram of body weight) given intravenously, while in the cat convulsions occurred even when the animal was completely anesthetized with pentobarbital sodium (35 mg. per kilogram of body weight intraperitoneally) before injection of the fluoroacetate.

Quin and Clark,[8h] in studying the poison of "gifblaar" (potassium fluoroacetate) in sheep and rabbits concluded that it was a cardiac poison affecting the conducting mechanism, thus leading to partial or complete heart block.

Thus, from the experimental work with animals, an array of responses has been obtained which encompasses completely the clinical picture seen in the present case of human poisoning. In spite of the lack of electrocardiographic records during the moments of maximal cardiac irregularity, premature ventricular contractions and totally irregular rhythm were noted. Accentuated T waves appeared in the electrocardiogram. Preliminary retching and vomiting, followed by carpopedal spasm and, later, by convulsive episodes with intervening flaccidity, and periods of myotonic convulsions with interspersed violent myoclonic convulsions occurred much as they were described in experimental poisoning in the cat. Episodes of complete respiratory cessation during the convulsive period, quite similar to the apnea described in many animals (particularly the pig), occurred twice in the present case and may have ended fatally had artificial respiration not been employed. Recovery, as it was with experimental animals, was complete without sequelae. From the present case it appears that the human species falls into Chenoweth and Gilman's group II (cat, pig, rhesus monkey) with both cardiac and central nervous system effects.

No electroencephalographic records were made during the child's illness. Ward [5c] studied the central nervous stimulation produced by fluoroacetate and observed local, rhythmic seizure discharges in subcortical structures at the time severe tonic seizures were present in the animals (cats). He concluded that the major locus of action is subcortical and that the cortical petit mal type of response (spike and dome waves of high voltage at a rate of 3 per second) in the electroencephalogram observed by Chenoweth and St. John,[5d,e] and also occasionally by Ward himself, was of secondary importance. Ward found no clear correlation of the electrical activity of the cortex with the paroxysmal activity in the thalamus, hypothalamus or reticular formation of the pons.

Several studies of the biochemical mechanism underlying the toxicity of fluoroacetate have been made. Bartlett and Barron [6] advanced the hypothesis that fluoroacetate is a competitive inhibitor for biochemical reactions in which acetate takes part. Liebecq and Peters [7] recently further investigated this hypothesis and observed that an additional hypothesis was necessary: Fluoroacetate is transformed into another substance which is inhibitory to the tricarboxylic cycle, thereby causing accumulation of citrate. Neither group of workers observed a single enzyme reaction inhibited by fluoroacetate to explain the fact that this substance stops carbohydrate oxidation in the tricarboxylic acid cycle.

CONCLUSIONS

Human poisoning with fluoroacetate further reflects the species differences in the clinical picture presented which many other mammals with experimental poisoning have previously revealed. Cardiac and central nervous system effects are both important, the central nervous system effects predominating. This renders the clinical picture somewhat similar to that observed in the cat, pig and rhesus monkey, but most like that in the cat.

No antidote is available for the poisoning, but sedation with barbiturates offers a possible means of combating the convulsions. Because of the danger of respiratory depression and cessation, a respirator should be kept on hand and artificial respiration started immediately if prolonged apnea appears.

One cannot be certain whether the calcium therapy given early in the clinical course really influenced the outcome of the present case or

6. Bartlett, G. R., and Barron, E. S. G.: Effect of Fluoroacetate on Enzymes and on Tissue Metabolism: Its Use for Study of Oxidative Pathway of Pyruvate Metabolism, J. Biol. Chem. **170**:67 (Sept.) 1947.

7. Liebecq, C., and Peters, R. A.: The Toxicity of Fluoroacetate and the Tricarboxylic Acid Cycle, Biochem. Biophys. Acta **3**:215 (April) 1949.

not. However, the notable relaxation from the tonic tetany-like state in which the patient was admitted and the immediate improvement associated with administration of calcium gluconate (intravenously) warrant its use again in any future cases.

Should ventricular fibrillation occur, the experimental experience of Chenoweth and Gilman with monkeys warrants the intracardiac use of procaine hydrochloride and cardiac massage.

It should constantly be remembered that supportive and symptomatic therapy alone is available; however, if the patient is carefully observed and emergencies handled as they appear, complete recovery without sequelae is possible.

SUMMARY

Sodium fluoroacetate, commonly called "1080," has obtained widespread use since the war as a potent rodenticide. Because of its varied pharmacologic properties and biochemical interest, it has become increasingly important in laboratory studies. Experimental poisoning in laboratory animals was studied during and since the war by many workers, but no previous report of a case of human poisoning is known to us.

A case of poisoning with what was probably relatively pure sodium fluoroacetate in a 2 year old Negro child is reported. Cardiac and central nervous system symptoms predominated, as in experimental animals, but the child recovered completely without sequelae.

The clinical picture presented by this case is briefly compared with that seen in experimental poisoning, and the literature on fluoroacetate poisoning is briefly reviewed.

NOTE.—Since this paper was submitted for publication, we have noted in an article by Hutchens and his associates [8] reference to a case of this poisoning in a child (from a personal communication to the authors by Dr. Eleanore R. Wright) whose convulsions were controlled with pentobarbital sodium and who was also given ethanol. The child survived. These workers reported decreased mortality due to fluoroacetate poisoning in mice, guinea pigs and rabbits treated with 10 per cent solution of ethanol in isotonic sodium chloride solution given subcutaneously within ten minutes of injection of the poison. The mechanism of competitive inhibition of acetate reactions suggested this form of therapy. Its value in human cases is unknown.

Dr. Francis F. Heyroth and Dr. Henry W. Ryder, of the Kettering Laboratory of Applied Physiology, Cincinnati, assisted with the case here presented.

Children's Hospital, Boston (Dr. Gajdusek).

8. Hutchens, J. O.; Wagner, H.; Podolosky, B., and McMahon, T. M.: The Effect of Ethanol and Various Metabolites on Fluoroacetate Poisoning, J. Pharmacol. & Exper. Therap. **95**:62, 1949.

Case Reports

TERATOMA OF THE OVARY IN AN INFANT TWENTY MONTHS OF AGE

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THIS is a report of a teratoma of the ovary discovered during a routine examination of a 20 month old baby girl and successfully removed at operation. The occurrence of this tumor in a child so young is rare indeed; the youngest previously recorded patient was 3 years of age.

REPORT OF A CASE

Patient T. K. was the first born of a woman 28 years of age. Delivery was by cesarean section, the indication being a general contraction of the pelvis with breech presentation. The child appeared normal at birth and was bottle fed. She thrived well with no illnesses other than two "colds." Immunizations against diphtheria and whooping cough were given separately.

At the age of 20 months on routine examination, a smooth ovoid mass, the size of a large egg, was noted in the suprapubic region, exactly in the midline vertical with the long axis. It extended almost to the umbilicus. The tumor was freely movable and could be manipulated to any part of the abdomen without discomfort to the patient. One gained the impression that slightly more effort was required to hold it up to the right costal margin than to the left. After activity of the patient, the growth always returned to the same midline position just above the symphysis pubis. Other than these findings neither the physical examination nor the laboratory reports revealed anything of special interest. There were no complaints.

The child was observed for seven months, during which the mass seemed to increase in size. When she was 27 months old, operation was performed with the patient under ether anesthesia. The tumor was easily removed through a left midrectus incision. It apparently originated in the left ovary which had been replaced. The fallopian tube was not removed. Recovery was rapid and uneventful.

Pathologist's Report (Dr. H. J. Linn).—Gross Description: The specimen was a smooth-walled, rounded cyst, measuring 8 by 9.8 by 6.5 cm. Scattered over the serosal surface were seven slightly raised, smooth areas, measuring up to 5 mm. in diameter. On section the cyst was filled with straw-colored fluid. Its lining was smooth except near the attachment of the ovary where there was a cluster of rounded raised masses which, at one place, were confluent. Each mass measured 2 cm. in greatest diameter and together they covered an area in the wall measuring 5.5 by 2.5 cm. They projected from the remainder of the wall 1.2 cm. into the lumen. On section the lumen of these smooth nodules

From the Burnham City Hospital.

in the wall of the cyst communicated. The lumen was filled with yellow cheesy material and grayish yellow creamy fluid in which there was yellow hair.

Microscopic Description: The large cyst was lined by low cuboidal epithelium, in places forming tall papillary processes. The small cysts were lined with stratified squamous epithelium and in the wall were many sebaceous glands, cartilage, bone and fatty tissue. In one place there was a thin shell of brain tissue, which in its center was liquefied. No evidence of malignancy was seen.

The diagnosis was (1) papillary serous cyst of the ovary and (2) teratoma of the ovary.

Photomicrograph of teratoma of ovary, showing island of cartilage, sebaceous glands and stratified squamous epithelium.

COMMENT

The long-accepted definition of a teratoma as a tumor composed of tissue derived from two or more germ layers has been questioned by some pathologists.[1] They point out that tumors classified as dermoids may contain fragments of tissue from two or more germ layers. Several attempts have been made to set up criteria for accurately separating teratomas and dermoids, but none are entirely satisfactory.

Both teratomas and dermoids, however, are rarely found as ovarian tumors in young children. Harris[2] collected reports of 21 cases of teratoma of the ovary

1. Moore, R. A.: A Textbook of Pathology, ed. 1, Philadelphia, W. B. Saunders Company, 1944, p. 1119.

2. Harris, R. H.: Carcinomatous Ovarian Teratoma with Premature Puberity and Precocious Somatic Development, Surg., Gynec. & Obst. **24**:604, 1917.

in patients under 14 years. The youngest were 3 years and 3 years 8 months of age, respectively. Ladd and Gross [3] wrote of a teratoma of the ovary in a child of 6 years and of a dermoid in another child of the same age. German [4] described a fetal teratoma in a child 6 years 10 months of age. Mazzola and Ryan [5] reported a dermoid cyst in a girl, aged 5 years.

The consensus is that ovarian tumors in children should be removed promptly to avoid the possibility of the development of malignancy in a benign growth.

SUMMARY

Herewith is reported the unusual occurrence of a teratoma of the ovary in a girl 20 months of age. The growth was successfully removed. The next youngest children with this tumor for whom records were found were 3, 3½, 6 and 6½ years of age, respectively.

311 West University Avenue.

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MASKED MUMPS ENCEPHALITIS COMPLICATED BY HEMIPLEGIA

HARRY BLOCH, M.D.
DANIEL HIRSCHL, M.D.
RICHARD TURIN, M.D.
AND
BERNHARD ZALEZNAK, M.D.
BROOKLYN

Mumps encephalitis is not uncommon and is generally considered a mild disease. Death is rare, and recovery is usually rapid and complete.[1]

However, two facts disturb present complacency with regard to the prognosis of mumps encephalitis. First, there have been reports[2] of severe neurologic sequelae: viz., involvement of the third, sixth and seventh cranial nerves, polyneuritis, optic atrophy, deafness, ascending myelitis, hemianopsia, hemianesthesia, complete deviation of the eyes, chorea, myoclonus, ataxia and personality changes. Second, since it is an accepted fact that mumps encephalitis may occur without apparent infection of the salivary glands, instances of masked mumps encephalitis with severe neurologic sequelae may go undiagnosed under the general classification of encephalitis.

In the absence of painful enlargement of the salivary glands or of inflammation of the gonads, the diagnosis of masked mumps encephalitis becomes a problem. When obtainable, a history of contact is valuable. However, results of laboratory procedures, such as the complement fixation tests for antibodies,[3] are conclusive.

It is the purpose of this paper to report a case of masked mumps encephalitis which illustrates: (1) the absence of clinical evidence of involvement of the salivary

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From the Pediatric Service, the Beth-El Hospital.

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2. McKaig, C. B., and Woltman, H. W.: Neurological Complications of Epidemic Parotitis: Report of Case of Parotic Myelitis, Arch. Neurol. & Psychiat. **31**:794 (April) 1934. Findlay, J. W.: Case of Infantile Hemiplegia (Acute Cerebral Palsy of Childhood) Which Followed Mumps, Glasgow M. J. **65**:50, 1906. Eley, R. C.: Neurologic Conditions in Infants and Children, J. Pediat. **7**:248, 1935. Ford, F. R.: Disease of the Nervous System in Infancy, Childhood and Adolescence, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1944.

3. (*a*) Kane, L. W., and Enders, J. F.: Immunity in Mumps: The Complement Fixation Test as an Aid in the Diagnosis of Mumps Meningoencephalitis, J. Exper. Med. **81**:137, 1945. (*b*) Henle, G.; Henle, W., and Harris, S.: Serological Differentiation of Mumps Complement Fixation Antigens, Proc. Soc. Exper. Biol. & Med. **64**:290, 1947; (*c*) The Use of Complement-Fixation Technic in the Analysis of Two Institutional Outbreaks of Mumps, Pediatrics, **1**:593, 1948.

glands or gonads; (2) a serious neurologic sequela, hemiplegia, and (3) the value of the complement fixation test of Henle, Henle and Harris,[2b, c] for the early positive identification of encephalitis due to the mumps virus.

REPORT OF A CASE

A white girl 16 months of age was admitted to the Beth-El Hospital on July 6, 1948.

On her admission, the child was unconscious and having frequent severe convulsions. The temperature was 106 F. The pupils were unequal and reacted to light. There was a bilateral nystagmus to the left. The neck was flaccid. The Brudzinski, Babinski and Kernig signs were not elicited. The deep tendon and superficial abdominal reflexes were absent. There was no enlargement of the salivary glands.

The mother reported that the onset was sudden, occurring six hours before admission, with convulsions and fever. Two weeks prior to the child's admission there was contact with a sibling who had mumps. On her admission, the spinal fluid appeared hazy and revealed a pleocytosis (440 white blood cells), with lymphocytes predominating. The reaction to the Pandy test for increased globulin in the spinal fluid was positive. Culture and smear of the spinal fluid did not reveal any bacteria. The blood count showed 12,000 white blood cells, with 62 per cent lymphocytes, 3 per cent monocytes and 35 per cent polymorphonuclear leukocytes.

For four days the course of the child's illness was hectic. A flaccid paralysis of the left arm and leg was observed soon after her admission. The temperature ranged from 101 to 106 F. Convulsions were frequent, and the child was almost constantly comatose. Treatment consisted of fluids intravenously, penicillin intramuscularly and sulfadiazine by hypodermoclysis. On the fifth day, the fever and convulsions subsided. The child appeared more alert. However, the flaccid paralysis of the left arm and leg was unchanged.

Examination three months after onset revealed residual left hemiplegia.

The complement fixation tests for antibodies in this patient were done by Henle and his co-workers. Blood taken on the day following admission, July 7, contained antibodies against S antigen in a titer of 1:64 and against the V antigen in a titer of 1:4. Titers of 1:4 or less are of no significance. A second specimen of blood, examined on July 22, demonstrated an increase in titer against both the S and the V antigens to 1:512.

COMMENT

On her admission the condition of our patient was diagnosed as encephalitis. A history of contact with mumps suggested the likelihood of a masked mumps encephalitis. The recent reports of Henle, Henle and Harris[2b, c] suggested a rapid method for establishing the diagnosis. The results of this test identified the mumps virus as the etiologic factor for the encephalitis.

CONCLUSION

We have presented a case of masked mumps encephalitis without involvement of salivary glands or gonads. The onset was fulminating, with high temperature, convulsions and coma.

The complement fixation test of Henle, Henle and Harris identified the etiologic agent.

The child was left with a serious neurologic sequela, hemiplegia.

1745 President Street (13).

ALTERNATION IN THE ELECTROCARDIOGRAM OF A THREE AND ONE-HALF MONTH OLD INFANT

BRUNO KISCH, M.D.
AND
B. RICHMAN, M.D.
NEW YORK

Alternation in the electrocardiogram is only occasionally seen in patients with pulsus alternans. Furthermore, it may occur without alternation in the peripheral pulse.[1]

In children alternation in the electrocardiogram has rarely been reported. In 1917, Windle [2] recorded alternation in a boy 13 years of age following treatment with digitalis. In a series of 16 patients Kalter and Grishman [3] reported alternation in 3 children under 13 years of age, the youngest being 5 years old. In these 3 children only alternation of the QRS complex was reported. Unfortunately, none of the tracings were reproduced in their paper.

Nádrai [4] mentioned alternation in the electrocardiogram (his fig. 24) in a child 9 months old with situs inversus and truncus arteriosus communis. The child died soon afterward. As far as we know, this is the earliest age at which alternation has been observed.

Alternation in the electrocardiogram, especially in patients with a high degree of tachycardia, may be observed more frequently in the future, since the recording of chest leads has become a routine procedure in clinical cardiologic practice. As one of us (B. K.) showed previously,[5] alternation may be absent in standard leads but is readily discernible in some of the chest leads.

In the following report an electrocardiogram is presented disclosing conspicuous alternation of the R, S and T waves, which was recorded in a 3½ month old infant convalescing from bronchopneumonia.

REPORT OF A CASE

This child, weighing 6 pounds 2 ounces (2,778 Gm.), was born Oct. 3, 1948 and was admitted to the pediatric service of the Mount Sinai Hospital on Jan. 15, 1949, with bronchopneumonia. When admitted, it weighed 11 pounds 10 ounces (5,273 Gm.). The temperature was 101 F. The white blood cell count was 10,500;

From the Cardiographic Department of the Mount Sinai Hospital (Dr. A. M. Master, director).

1. Kisch, B.: Ergebnisse der Kreislaufforschung: Der Herzalternans, Dresden, Theodor Steinkopff, 1932, vol. 2.

2. Windle, J. D.: The Effect of Digitalis in Heart Disease, Quart. J. Med. **10**:274, 1917.

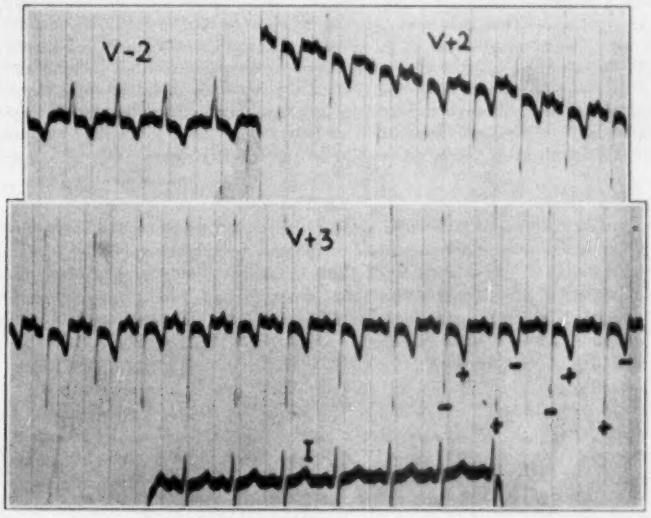
3. Kalter, H., and Grishman, A.: The Electrical Alternans, J. Mt. Sinai Hosp. **10**:459, 1943.

4. Nádrai, A.: Die Elektrokardiographie im Säuglings- und Kindesalter, Ergebn. d. inn. Med. u. Kinderh. **60**:688, 1941.

5. Kisch, B.: A Contribution to the Problem of the Electrical Alternation, Cardiologia **6**:95, 1942.

the hemoglobin concentration was 7 Gm. per hundred cubic centimeters, and the hematocrit reading was 32 per cent. The urine was clear. Roentgenologic examination showed infiltration in the upper lobe of the left lung and in the lower and upper lobes of the right lung.

The child received 150,000 units of penicillin twice daily and 0.2 Gm. of sulfadiazine and was kept in an oxygen tent. On January 18, the condition was much improved and the temperature fairly normal. On January 21, the medication was discontinued and the oxygen tent removed. The temperature was 98.5 F., and, when the child was quiet, the pulse rate was 150 and the respiratory rate 40. At that time our electrocardiographic tracings were taken. A few days later the child was dismissed from the hospital as fully recovered, and has been well since.



Electrocardiographic tracings of infant 3½ months old showing alternation in the R, S and T waves of lead V + 3.

The Electrocardiogram.—The child was excited at the time the records were taken; therefore, only short pieces of the electrocardiogram were suitable for analysis.

A sinus tachycardia, with a rate of 160 to 170 per minute, was present. No alternation was noticeable in any of the waves in leads I, II and III, or in the chest leads taken on the right side.

All chest leads were taken as V leads. If the electrode was placed at the right midclavicular line (V — 3 according to our nomenclature) [6] or at the right border of the sternum (V — 2), no alternation was present. However, at the left sternal

6. Kisch, B.: The Chest Lead Diagram (CLD), Exper. Med. & Surg. **4**:vi, 1946; New Applications of Chest Lead Diagrams, ibid. **7**:1, 1949.

border (V + 2) alternation of the T wave could be noticed. Alternation of the S wave may also have been present but cannot be definitely ascertained because the tracing is not technically perfect (fig.).

In lead V + 3 we were fortunate enough to register a good tracing of five seconds' duration. The lower tracing, lead I, was taken simultaneously. Lead I shows no alternation; however, in position V + 3 the alternation of R, S and T waves is clearly visible. As is well known from other cases in man and from animal experiments, in alternation the larger T wave may be present in the beats with the smaller R and S waves and vice versa. That is also the case in our tracing.

COMMENT

This is the first recorded instance of alternation in the electrocardiogram in a healthy infant. Although it is well known [1] that in tachycardia alternation may appear without serious prognosis, it has never been observed in a child 3½ months of age. The respiratory rate of the present child was about 40 to 50 per minute. This excludes the possibility of a pseudoalternation due to interference of breathing.[1]

It is especially noteworthy that this child was not ill at the time the observation was made, although convalescing from pneumonia. The influence of drugs on the heart in this case is improbable but cannot be excluded, as the child received penicillin and sulfadiazine up to the day the tracings were taken.

SUMMARY

A child 14 weeks of age with a heart rate of 160 to 170 and a respiratory rate of 50, convalescing from pneumonia, showed an alternation of R, S and T waves in several of the chest leads. This is the first time that alternation has been registered in an infant of this age.

845 West End Avenue.

News and Comment

GENERAL NEWS

Additional Mead Johnson Fellows Appointed.—The Society for Pediatric Research announces the appointment of seven additional Mead Johnson fellows for the academic year 1949-1950, as follows: Dr. C. T. Lee, China; Dr. Solomon A. Kaplan, Union of South Africa; Dr. Carlos A. Bauza, Uruguay; Dr. Isabelle Valadian, Lebanon; Dr. Ramon Sanz Munoz, Mexico; Dr. Dacio Pinheiro, Brazil, and Dr. Jorge Arguedas Soto, Costa Rica.

Benjamin Knox Rachford Lectureship.—Dr. Lawson Wilkins, of Baltimore, will deliver the eighteenth annual series of the Benjamin Knox Rachford Lectureships on Tuesday, Feb. 7, and on Wednesday, Feb. 8, 1950, at 8:30 p. m. in the auditorium of the Children's Hospital Clinic and Research Building, Cincinnati. His lectures will deal with the role of hormones in the regulation of somatic and sexual development.

Physicians Certified by the American Board of Pediatrics, Inc.—The following physicians were certified as specialists by the American Board of Pediatrics, Inc., after examinations held at Brooklyn, Oct. 21, 22 and 23, 1949. Jerome Seymour Beloff, Meriden, Conn.; Thomas D. Benson, Rochester, N. Y.; Sidney Borow, Philadelphia; Philip Briscoe, Annapolis, Md.; John Brandon Castiglione, Visalia, Calif.; Albert Cohen, Cambridge, Mass.; Peter Alexander Duncan, Port Chester, N. Y.; Samuel E. Elmore Jr., Spartanburg, S. C.; Harold Y. Finck, Washington, D. C.; Martin Harwin, Brooklyn; Frederic Hertzmark, Dorchester, Mass.; Martin H. Jacobs, Forest Hills, N. Y.; Frank W. Kibbe, Lincolnville, Maine; Robert Koenigstein, Staten Island, N. Y.; Steven Ellis Koweity, Franklin Square, Long Island, N. Y.; Margaret Morgan Lawrence, Corona, N. Y.; Fernando R. Leyva, Washington, D. C.; Laura L. Lipscomb, Atlanta, Ga.; Herman Lubenstein, Bronx, N. Y.; Harold S. Medoff, Philadelphia; Thomas M. Monagan, Waterbury, Conn.; Irving Nelson, Hartsdale, N. Y.; Arnold Paul Nicosia, Manhasset, Long Island, N. Y.; George Saxon Palmer, Tallahasse, Fla.; Charles Frank Payton, Royal Oak, Mich.; Louis Arthur Perillo, Perth Amboy, N. J.; Gerald J. Piserchia, Belleville, N. J.; Alexander Randall, Philadelphia; Arthur J. Rich, Sun Valley, Calif.; Homer R. Rich, Ogden, Utah; Joseph Robinson, Wilkes-Barre, Pa.; Sydney Ross, Washington, D. C.; John J. Ryan, Waltham, Mass.; Steven Sawchuk, Philadelphia; Charles Frederick Scholhamer, New Haven, Conn.; Frank W. Shaffer, Norristown, Pa.; Robert Traill Shipman, Jersey City, N. J.; Leslie Byron Silverstine, Bradford, Pa.; S. Harvey Sklar, Cliffside Park, N. J.; Jack M. Spitalny, Albany, N. Y.; Frederick Harris Stiefel, Brooklyn; Ralph S. Stiller, Alexandria, Va.; Henry Herbert Stroud, Wilmington, Del.; Edward Sydney Szelewa, Newark, N. J.; Henry C. Thacher, Auburn, Maine; Charles Varga, New York; John T. Walke, Roanoke, Va.; Alvah Marvin Weiss, Peekskill, N. Y., and William Hodge Wood Jr., Charlottesville, Va.

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

A Comparison of Effect of Carbonamide and Benzoic Acid on Penicillin Plasma Concentrations. William P. Boger and Richard M. Baker, Proc. Soc. Exper. Biol. & Med. **66**:1 (Oct.) 1947.

Seven persons without fever or evidence of renal, hepatic or cardiac disease were studied for three different periods following the administration of 200,000 units of penicillin G dissolved in 2 cc. of sterile water. One injection was given at 6 a.m. and another at 9 a.m., after which blood specimens were obtained for penicillin assay at fifteen, thirty, sixty, one hundred and twenty and one hundred and eighty minutes. Each person had a control period followed by one in which he received 16 to 24 Gm. of benzoic acid in divided doses every three hours. The drug was given for the day preceding the study, as well as during the time of the study. A similar course was followed with carinamide, employing essentially the same dosage. The administration of benzoic acid was observed to have no effect on the penicillin plasma concentration, whereas carinamide given to the same patients in the same doses caused a uniform and notable enhancing effect, averaging five times the control values. Hansen, Galveston, Texas.

Variants of Escherichia Coli, Pseudomonas Aeruginosa and Bacillus Subtilis Requiring Streptomycin. T. Kushnick, C. I. Randler, C. T. Gray and J. M. Birkeland, Science **106**:587 (Dec. 12) 1947.

The phenomenon, as described by Miller for the Meningococcus, of bacterial variation in the direction of requiring streptomycin for growth, has been noted by the authors in strains of three additional organisms, Escherichia coli, Pseudomonas aeruginosa and Bacillus subtilis. Strains of the three organisms, which developed resistance to concentrations of streptomycin of the order of 1,000 to 8,000 micrograms per cubic centimeter when grown on mediums containing the antibiotic, were observed to have a better and more rapid growth in the presence of streptomycin. Other organisms exhibiting this peculiar property of streptomycin dependence will in all probability be found. Clinical implications of this phenomenon are clear. Forbes, St. Louis.

Metabolism; Infant Feeding; Milk and Other Foods

The Relation Between the Serum Urea Concentration and the Protein Consumption of Normal Individuals. T. Addis, E. Barrett, L. J. Poo and D. W. Yuen, J. Clin. Investigation **26**:869 (Sept.) 1947.

Measurements of serum urea concentration were made on 10 medical students during periods of varying protein intakes. While they had a daily protein intake of 0.5 Gm. per kilogram of body weight, the average blood urea concentration in 120 determinations was 19.3 mg. per hundred cubic centimeters, with a standard deviation of 2.9. While they received 1.5 Gm. per kilogram of body weight, the average serum urea level was 38.6 mg. per hundred cubic centimeters (60 observa-

tions), with a standard deviation of 7.1, and, when the protein consumption was increased to 2.5 Gm. per kilogram of body weight per day, the average serum urea concentration was 45.5 mg. per hundred cubic centimeters, with a standard deviation of 7.2.

The subjects all received more than 2,000 calories daily on all dietary regimens. The authors do not mention the effect of variation in fluid intakes of the subjects. The ability to predict statistically from serum urea concentrations the efficiency of the kidneys in clearing the blood of urea was discussed.

BRODSKY, Cincinnati.

SIGNIFICANCE OF LACTOSE IN INFANT FEEDING. E. MÜLLER, Ztschr. f. Kinderh. **65**:269, 1947.

For many years, German pediatricians used vegetable sugar in artificial feeding for infants because they seemed to obtain better gains in weight in their children with these sugars than with animal sugar (lactose). This opinion is not uniformly shared, and particularly several American authors (Gerstenberger and Ruh) have attributed to lactose a good influence on the gain in weight of infants. Bessau, in Germany, was of the opinion that lactose offered a certain protection against diarrhea because of its influence on the flora of the intestinal tract. The present author discusses in detail the chemical composition of lactose and its changes in the course of preparation and digestion. He comes to the conclusion that the value of lactose in infant feeding has been underestimated. Its importance lies not alone in its caloric value, which is lower than that of vegetable sugars, but, particularly, in the fact that its use permits the increased addition of fat to infant food without the dangers of diarrhea.

GLASER, Chicago.

Vitamins; Avitaminoses

PHYSIOLOGICAL AVAILABILITY OF THE VITAMINS: IX. INFLUENCE OF ASCORBIC ACID STABILIZERS IN FRUITS AND VEGETABLES. DANIEL MELNICK, MELVIN HOCHBERG and BERNARD L. OSER, J. Nutrition **34**:409 (Oct.) 1947.

Ascorbic acid is far more stable in fruit juices than in aqueous solutions, according to Melnick and his associates. The stabilizing factors in fruits and vegetables which protect ascorbic acid in vitro are ineffective, in the digestve system, in increasing ascorbic acid availability. Apple juice is a favorable vehicle for ascorbic acid in the human diet.

FREDEEN, Kansas City, Mo.

INTOXICATION FROM VITAMIN D_2. ALESSANDRO BIEBER, Riv. clin. pediat. **46**:98 (Feb.) 1948.

The author reports a clinical picture, consisting of anorexia, polydipsia, polyuria with typical symptoms of a disorder of the nervous system (apathy, abulia and indifference to surroundings) and a serious state of cachexia and dehydration, due to high doses of vitamin D_2 (1,000,000 international units every other day up to 13,000,000 units). This clinical picture is similar to that observed by other authors in such cases. The author mentions that among the little known modifications caused by excessive doses of vitamin D_2 is a sudden change of the physicochemical balance of the blood and an early functional alteration of the nervous centers, the complex and disturbed activity of which might explain, on one hand, the lack of regulation of the water metabolism, which already exists before the renal

changes, and, on the other hand, the nature of the cachexia and anorexia (the diencephalohypophysial system in its humoral and nervous function).

Second, and this was proved by the clinical course, the variations in calcemia require a quantity of calcium higher than the amount introduced, for which reason the calcium of the skeleton, controlled by the parathyroid glands, is also mobilized, causing a great tendency toward calcium deposition in the tissues (calcinosis), especially in the kidneys, with diminution of function until an acute renal insufficiency incompatible with life is reached. The author mentions the importance of the relation of vitamins to hormones (thymus) which experimentally and clinically analyzed might explain the different degrees of individual toxicity.

FROM THE AUTHOR'S SUMMARY.

Hygiene; Growth and Nutrition; Public Health

THE FIRST TWO YEARS OF THE BREAST-MILK BANK IN COPENHAGEN, DENMARK. J. FLAMAND CHRISTENSEN, Ugesk. f. læger **108**:443 (May 2) 1946.

The amount of breast milk collected from 382 mothers was 11,580 liters. At present, 22 to 24 liters are collected each day from 47 mothers, which represents 300 cc. per mother. The highest amount of breast milk delivered from one mother was 2.5 liters per day.

WALLGREN, Stockholm, Sweden.

PREVENTIVE CARE OF MOTHER AND CHILD IN SWEDEN. JUSTUS STRÖM, Nord. med. **31**:1560 (July 19) 1946.

The development of mother and child care under governmental management has since its first year, 1938, led to an organization which in 1945 comprised the entire population. During this period, the number of health centers increased from 73 to 1,194. Physicians, midwives, nurses and mothers with their children are given free transport to and from the centers. In 1944, 55 per cent of the mothers and 79 per cent of the infants were regularly supervised by the health centers. The pregnant women visited the centers 2 to 2.5 times during their pregnancy; the infants were examined four to five times annually. The nurses made, on an average, 6.5 visits to the home during the first year of the child's life, with fewer visits later. About 75 per cent of the infants were breast fed during the first two months of life, 42 to 46 per cent during the first six months. The incidence of rickets, tetany and serious nutritional disturbances showed a great decrease. Infant mortality was about 3 per cent in 1944.

WALLGREN, Stockholm, Sweden.

PRENATAL CARE. J. A. STROINK, Nederl. tijdschr. v. geneesk. **91**:3624 (Dec. 13) 1947.

The practice of prenatal care in the obstetric clinic of the University of Utrecht, Netherlands, under the direction of Professor de Snoo, resulted in, among 40,000 pregnant women seen in twenty years, only 1 death from intoxication and eclampsia. By means of external version of the fetus after the twenty-eighth week, the ratio of breech presentations diminished from 3 to 4 to 1.5 per hundred. In women with narrowness of the pelvis, abnormal presentations were corrected. There was a routine examination for syphilis and diabetes. Attention was paid to adequacy of diet, virus diseases and Rh blood grouping.

VAN CREVELD, Amsterdam, Netherlands.

Prematurity and Congenital Deformities

URACHAL FISTULA. TRYGVE KAHRS, Tidskr. f. d. norske lægefor. **66**:320 (May 15) 1946.

A boy 2½ years of age had at birth a sausage-shaped tumor 5 cm. long extending from the umbilicus below the cord. This malformation, which had a circular lumen in its center, fell off spontaneously during the neonatal period. A short time later, the mother observed that urine passed from the umbilicus, and, on examination of the child at 2½ years of age, a urachal fistula which could be sounded with a no. 14 Nélaton catheter was found. Occlusion of the fistula was performed. The child was discharged from the hospital in healthy condition.

WALLGREN, Stockholm, Sweden.

Newborn

KERNICTERUS. ROBERTO GIUNTINI, Riv. clin. pediat. **46**:1 (Jan.) 1948.

The author continued the studies and the clinical observations on kernicterus which he partially reported on in 1942. He now gives a completely new picture of this disease based, for the most part, on his clinical experience.

From the pathogenetic point of view he considers kernicterus as appearing solely as a result of severe icterus of the newborn, a condition which may be avoided only by transfusions of Rh-negative blood at an early stage, that is to say, at the beginning of the icterus. In addition, the accumulation and the persistence of bile pigments in the nuclear masses of the base of the brain are necessary and determinant causes for the production of irreversible nervous lesions and, therefore, of the clinical syndrome of kernicterus. For classification of the illness a single concept must be followed, embodying all the various forms under which the disease may occur, from the mildest to the most serious types, whether alterations of muscular tone or hyperkinetic movements prevail.

The author then gives details of the course of the illness in its various forms and the numerous phases and most characteristic aspects of the symptomatology. He analyzes the psychic state of these patients and concludes that a serious manifest impairment of the intelligence is not a part of the usual picture of kernicterus.

In comparison with other diseases of the extrapyramidal nervous system, kernicterus bears suggestive analogy to progressive lenticular degeneration (Wilson's disease), but kernicterus is etiologically different. There is reason, however, for the supposition of much closer etiologic relation with other extrapyramidal syndromes, especially Vogt's syndrome.

FROM THE AUTHOR'S ABSTRACT.

ERYTHROCYTOMETRIC FORMULA AND RETICULOCYTES IN NORMAL NEWBORN, PREMATURE AND ASPHYXIATED INFANTS. ALDO FERLAZZO, Riv. clin. pediat. **46**:386 (June) 1948.

The author studied the behavior of the erythrocytometric formula and reticulocytes in 12 newborn infants, 5 of whom were normal, 4 premature and 3 affected by asphyxia in the first hours of life, after forty-eight hours and after four, five and eight days.

The red cells fell into classes according to diameters of the cells expressed in microns. The percentages of cells of each class were recorded for these children. The author noted that the blood of the normal infants born at term and the ones with slight asphyxia at birth always contained more than five classes of red

cells, the diameter of which generally varied from a minimum of 6.56 microns to a maximum of 12.30 microns. In children in the second day of life the formula tended to change, with the changes becoming more pronounced in the following days, so that at the beginning of the second week of life, the class of cells with diameters of 8.20 microns included 50 per cent of the cells. This percentage approached that of the adult in good health. In the premature infant, anisocytosis and macrocytosis were more prominent and the changes more rapid than in the infant born at term.

In infants with serious asphyxia (white asphyxia) the alterations were less striking than in the normal newborn child.

The number of reticulocytes was slightly higher in these infants than in the older child and the adult and reached, in the premature infant and in those with serious asphyxia, the possible level of 12 to 13 per cent. The values decreased in the first days after birth, with a course generally parallel to that of the erythrocytometric formula.

FROM THE AUTHOR'S ABSTRACT.

Acute Contagious Diseases

GENESIS OF RHEUMATIC FEVER. WESLEY W. SPINK, Minnesota Med. **31**:267 (March) 1948.

In this paper an attempt is made to crystallize the available knowledge on the factors which precipitate acute rheumatic fever. The author discusses the role of infection, factors concerning the host and environmental factors under the heading of precipitation; then he goes on to discuss tissue reactions. His brief review indicates that many complicating elements enter into the elucidation of the problem of the genesis of rheumatic fever. Although there is more than suggestive evidence that the hemolytic streptococcus is responsible for some cases of rheumatic fever, the precise mechanism whereby this species of bacteria provokes the disease is not clearly understood. The most logical working hypothesis at present is that in some cases, at least, a hypersensitivity of the tissues to the hemolytic streptococcus exists. In addition, there are certain ill defined factors seen in the host, such as an inherited susceptibility of the tissues to this type of sensitivity.

STOESSER, Minneapolis.

TECHNIC OF EARLY MOBILIZATION IN ACUTE ANTERIOR POLIOMYELITIS. LELIO NASSI and MARIO PASTORINI, Riv. clin. pediat. **46**:33 (Jan.) 1948.

The authors report some details of a technic of early mobilization in patients with acute anterior poliomyelitis. The use of special elastic suspension allows the paralyzed limbs a sufficient and continuous motion and diminishes the force of gravity, thus lowering the tone of the antagonistic muscles. The results obtained with such a technic have been encouraging, as the method itself also helps in mental motive reeducation.

FROM THE AUTHORS' ABSTRACT.

POSTMEASLES ENCEPHALITIS. GINO BROGI and LANDO LANDUCCI, Riv. clin. pediat. **46**:83 (Feb.) 1948.

The authors, after mentioning the measles epidemic of March to August 1946, during which several cases of encephalitis were observed, report the cases of 4 children who were seriously ill and who were hospitalized in the pediatric clinic of Siena, Italy.

One of them is interesting on account of the observation of a parkinsonian-like catatonic syndrome, a condition which is uncommon in postmeasles encephalitis. The authors advance various pathogenetic theories to explain the nature of this disease, and they conclude that, although indisputable proof is not possible at present, they cannot reject in a categorical way the hypothesis of a latent virus in the organism.

They were led to this conclusion by various considerations, not the least important of which was their observation of the most remarkable effect of the serum of a little girl who had recovered from postmeasles encephalitis on a patient with a severe attack of the disease.

FROM THE AUTHORS' SUMMARY.

DIPHTHERITIC INTOXICATION: THE PHOSPHOLIPIDS IN THE THERAPY OF DIPHTHERIA. FERNANDA CHEMI, Riv. clin. pediat. **46**:279 (May) 1948.

Four hundred and five persons having diphtheria with various types of localization and of varying severity were examined. They were carefully followed, with special regard to the appearance of symptoms due to diphtheritic intoxication, and also in relation to the day of illness.

Of the aforementioned patients, 118 were treated with intravenous injections of "bioplastina" (a 5 per cent emulsion of lipids of yolk of egg in isotonic sodium chloride solution). A much more favorable course was noted in the patients treated in this manner.

FROM THE AUTHOR'S SUMMARY.

ABDOMINAL SYNDROMES OF RHEUMATIC DISEASE. LELIO NASSI and MARCELLO GIUSTI, Riv. clin. pediat. **46**:458 (July) 1948.

The authors, after carefully reviewing the literature on the subject, report their observations on 12 children with acute abdominal syndromes undoubtedly linked to rheumatic disease.

In regard to the genesis of such syndromes, they are of the opinion that peritoneal serositis intimately related to the infection itself is the most probable, but they do not exclude the possibility that syndromes of pain may sometimes depend on radiculitic manifestations, but only in those children in whom signs of nervous or meningeal symptoms of rheumatic origin are evident.

They draw attention to such abdominal syndromes in order to avoid making a diagnostic error in appendicitis. They are of the opinion that the pulse frequency and the absence of leukocytosis, or a moderate leukocyte count, in addition to the abdominal symptoms, are useful for differential diagnosis. The authors, moreover, stress the importance of an early diagnosis of this clinical picture of rheumatism before the stage of arthralgic symptoms, thus avoiding useless surgical operations. Such early diagnosis permits much more efficacious prophylaxis of rheumatic endocarditis, such as that advised by Prof. C. Cocchi with penicillin, sulfadiazine, salicylates and vitamin A.

FROM THE AUTHORS' SUMMARY.

THE FAMILIAL INCIDENCE OF RHEUMATIC FEVER: I. A DISCUSSION OF THE RELATIONSHIP BETWEEN A POSITIVE FAMILY HISTORY AND THE DEVELOPMENT OF RHEUMATIC FEVER IN INDIVIDUALS OF MILITARY AGE. G. C. GRIFFITH, F. J. MOORE, S. MCGINN and R. S. COSBY, Am. Heart J. **35**:438 (March) 1948.

Four groups of young adults were interviewed. Data on one group of patients with rheumatic fever (3,594) and on three groups of nonrheumatic persons (1,397), serving as controls, formed the basis of the study. Group 1 showed that approxi-

mately 78 per cent of the patients with "initial" rheumatic fever acquired the disease after separation from the family. The authors raise the question whether this indicates some agent outside the family as the chief factor operative in the causation of rheumatic fever. The tuberculous patients and the healthy persons who had had "initial" attacks of rheumatic fever while at home did not have secondary attacks after separation from the family.

It was noted in groups 2, 3 and 4, the controls, that the persons who had rheumatic fever prior to separation from the family showed a similar family incidence, and that this incidence did not differ greatly from that recorded in the rheumatic patients studied. The high familial incidence of rheumatic fever, averaging 44.7 per cent in those who had the disease while still at home, seems to indicate that there is some factor within the family. Is this factor a hereditary susceptibility of contact with the inciting agent in the home? The great need for further data on the subject of heredity versus environment is evident.

FROM THE AUTHORS' SUMMARY.

THE FAMILIAL INCIDENCE OF RHEUMATIC FEVER: II. A STATISTICAL STUDY OF THE FAMILIAL AND PERSONAL HISTORY OF RHEUMATIC FEVER. G. C. GRIFFITH, F. J. MOORE, S. MCGINN and R. S. COSBY, Am. Heart J. **35**:444 (March) 1948.

Three per cent of those persons making up the normal control groups had a personal history of rheumatic fever earlier in life. An attack of rheumatic fever earlier in life tended to facilitate a later attack, but this difference was not great. The occurrence of rheumatic fever in the family increased the risk of the person's having the disease while still in contact with the family, but not after he was separated from the family. There did not, therefore, appears to be a strong and inherited susceptibility. The occurrence of multiple cases in families could be explained on the basis of either common environment or contagion. In the light of the widely accepted relationship of streptococcic infection to rheumatic fever, and the lack of agreement concerning the roles of social, economic and geographic factors, the authors prefer to look on these data as indicating the dominant role of contagion in the development of rheumatic fever.

FROM THE AUTHORS' SUMMARY.

Chronic Infectious Diseases

TUBERCULOUS MENINGITIS. J. SCHWARTZ, Am. Rev. Tuberc. **57**:63 (Jan.) 1948.

Miliary tuberculosis develops, as a rule, a short time after the first infection. This is the principal reason the majority of cases of meningitis are observed in childhood. Infection of the meninges with the tubercle bacillus is rarely caused by direct infection from the blood stream, tubercles in the dura or discharging foci in the choroid plexus. Tuberculous meningitis is usually caused by infection of the subarachnoid space or the ventricles by cerebral or meningeal tuberculomas. Infection from even deep-seated tuberculomas may reach the brain surface or the ventricles by drainage through the periarterial lymph spaces. Caseous tuberculomas may occasionally be the source of hematogenous dissemination if the bacilli find their way into the lumen of a vessel.

SMITH, Ogden, Utah.

SEMINAR ON BCG. HENRY C. SWEANY, Am. Rev. Tuberc. **57**:95 (Jan.) 1948.

The highly controversial subject of the value of BCG vaccination in antituberculosis work was discussed pro and con at the meeting of the Medical Section

of the National Tuberculosis Association in San Francisco in June 1947. The panel consisted of Joseph D. Aronson, J. C. Geiger, Herman Hilleboe, Johannes Holm (Denmark), J. Arthur Myers and Sol Roy Rosenthal. As may be surmised, there was no agreement among these speakers concerning its value. The remarks of the moderator, Henry C. Sweany, summarize the collective views expressed, as well as opinions gained from other data. It has been proved beyond doubt that BCG vaccination is harmless and that it is feasible to administer the vaccine to human beings. BCG has a place in antituberculosis work if its use is rigidly supervised. The threshold of infectibility in the vaccinated persons is raised, better protecting them from infection. There may be a limited and temporary use in badly contaminated regions where public health facilities have collapsed to protect infants and young adults against the disease. In such a case it should be used only as a temporary measure, with complete supervision.

The indiscriminate use of the vaccine is undesirable for the following reasons: A false sense of security among both physicians and lay persons may develop, leading to the neglect of proved public health methods. Its cheapness may appeal to health officials who are attracted to the less expensive methods of prevention. Its use is unnecessary in most progressive countries where present methods of control are becoming more effective.

In localities where the incidence of tuberculin reactors is low, there is a distinct advantage in leaving those who are noninfective anergic, for the diagnosis not only of tuberculous infection but of nontuberculous diseases. It seems advisable not to create artificially positive reactions where not absolutely necessary.

In regard to the studies now in progress by the Tuberculous Control Division of the United States Public Health Service, Myers remarked that in such a highly scientific and thoroughly controlled study on a limited number of persons over a sufficiently long period, there is no danger of the development of a false sense of security among the public or neglect and abandonment of fundamental procedures.

SMITH, Ogden, Utah.

PRESENT POLICY OF THE AMERICAN TRUDEAU SOCIETY ON BCG VACCINATION. H. MCLEOD RIGGS, Am. Rev. Tuberc. **57**:543 (May) 1948.

BCG vaccine, prepared under ideal conditions and administered to tuberculin-negative persons by approved technics, can be considered harmless.

The degree of protection following vaccination is by no means complete nor is the duration of induced relative immunity permanent or predictable. The need for further basic research on the problem of artificial immunization against tuberculosis is recognized and is to be emphasized.

On the basis of studies reported, an appreciable reduction in the incidence of clinical tuberculosis may be anticipated when certain groups of persons who are likely to contract tuberculosis because of unusual exposure or inferior resistance, or both, are vaccinated.

Vaccination of the following more vulnerable groups of persons is recommended, provided they do not react to adequate tuberculin tests:

1. Medical personnel who are exposed to infectious tuberculosis

2. Hospital and laboratory workers whose work exposes them to contact with the bacillus of tuberculosis

3. Persons exposed to infectious tuberculosis in the home

4. Patients and employees of mental hospitals and prisons

5. Children and certain adults considered to have inferior resistance and living in communities in which the mortality rate from tuberculosis is unusually high.

Vaccination of the general population is not recommended at this time.

BCG vaccine should not be made available for general distribution in the United States at this time for reasons explained in this communication. The vaccine should be prepared only in accredited laboratories in which virulent tubercle bacilli are not cultivated or handled.

The society is of the opinion that, since BCG vaccine affords only incomplete rather than absolute protection, the most effective methods of control in the general population are (*a*) further improvement of living conditions and the general health, (*b*) reduction of tuberculous infection by modern public health methods, (*c*) prompt medical and surgical treatment of patients with the active disease, (*d*) segregation and custodial care of those not amenable to accepted forms of therapy and (*e*) adequate rehabilitation.

Vaccination seems unwarranted in (*a*) areas in which the tuberculosis mortality rate is extremely low and (*b*) localities in which the tuberculin test is of especial value as a differential diagnostic procedure.

SMITH, Ogden, Utah.

Diseases of Blood, Heart and Blood Vessels and Spleen

ON THE ETIOLOGY OF CLUBBING OF THE FINGERS. E. F. MAUER, Am. Heart J. **34**:852 (Dec.) 1947.

The author discusses the various theories concerning the causes of clubbing of the fingers and toes. He comes to the conclusion that for the development of clubbing low oxygen tensions must occur in tissues which are warm and in which the blood flow is greater than normal.

GIBSON, Chicago.

ATRIAL SEPTAL DEFECT: CORRELATION OF AUTOPSY FINDINGS WITH DATA OBTAINED BY RIGHT HEART CATHERIZATION. JOSEPH C. MASSEE, Am. J. M. Sc. **214**:248 (Sept.) 1947.

A case of interatrial septal defect and pulmonary vascular disease was studied by the method of catheterization of the right side of the heart.

HENSKE, Omaha.

A NEW TYPE OF HEREDITARY HEMOLYTIC JAUNDICE WITHOUT SPHEROCYTOSIS. RUSSELL L. HADEN, Am. J. M. Sc. **214**:255 (Sept.) 1947.

Eight patients in two families are reported on, all of whom had hemolytic anemia. The disease was observed in three generations in one family and in two generations in another, so that it appeared to be really hereditary. The red cells were of normal shape but tended to be macrocytic and to undergo spontaneous hemolysis. Hemoglobinemia was frequently observed. Splenectomy in the 1 patient operated on did not alter the course of the disease. The condition was probably due to an inherited defect in the stroma of the red cells. This disease seems to be a new type of hereditary hemolytic jaundice.

HENSKE, Omaha.

IDIOPATHIC THROMBOCYTOPENIC PURPURA: A STUDY OF THREE CASES WITH SPECIAL REFERENCE TO CHANGES IN THE MEGAKARYOCYTES. ELEANOR H. VALENTINE, Am. J. M. Sc. **214**:260 (Sept.) 1947.

In 11 control subjects the number of megakaryocytes showing evidence of thrombocyte production varied from 56 to 80 per cent with minimal degenerative changes. Three persons with idiopathic thrombopenic purpura showed a notable

depression of thrombocyte-forming activity by the megakaryocytes and a moderate increase in degenerated forms. Forty-eight hours after splenectomy thrombocyte production had returned to normal levels.

A sharp increase in thrombocytes occurred in all 3 patients after removal of the spleen, reaching a peak within ten days. This was followed by a temporary fall to thrombopenic levels, in 1 patient accompanied with a mild recurrence of purpura. In this patient moderate thrombopenia persisted and was apparently dependent on mild depression of megakaryocytic production of thrombocytes.

HENSKE, Omaha.

STUDIES ON THE ENIGMA OF THE HEMOSTATIC DYSFUNCTION OF HEMOPHILIA. ARMAND J. QUICK with the Technical Assistance of W. F. STAPP, Am. J. M. Sc. **214**:272 (Sept.) 1947.

Evidence is presented to show that the hemostatic dysfunction in hemophilia is due to a lack of available thromboplastin in the blood. This causes an insufficient production of thrombin, as shown by the fact that little prothrombin is consumed in the coagulation of hemophilic blood.

Results indicated that the thromboplastin of normal blood is present in the plasma in an inactive form designated as thromboplastinogen and is changed to active thromboplastin by the action of substances from the thrombocytes. The limitations of the coagulation time as an indicator of hemostatic efficiency are discussed. Coagulation is described as consisting of three fundamental steps: (1) the activation of thromboplastinogen, (2) the formation of thrombin and (3) the conversion of fibrinogen to fibrin.

HENSKE, Omaha.

STUDIES OF CRYOGLOBULINS: I. UNUSUAL PURPURA ASSOCIATED WITH THE PRESENCE OF A HIGH CONCENTRATION OF CRYOGLOBULIN (COLD PRECIPITABLE SERUM GLOBULIN). AARON BUNSEN LERNER and CECIL JAMES WATSON, Am. J. M. Sc. **214**:410 (Oct.) 1947.

An unusual case is reported in which purpura and sensitivity to cold were associated with a cold-precipitable serum protein. Similar cases previously reported are reviewed and discussed.

It is suggested that abnormal globulins may produce purpura, thrombosis, oozing of blood from mucous membranes and sensitivity to cold as a result of their concentration in the blood and, more particularly, their unusual solubility properties.

The term cryoglobulin is proposed to represent a group of proteins having the common property of precipitating (or jellifying) from cooled serum. If these proteins are in the serum in high concentration, they may precipitate spontaneously at room temperature.

HENSKE, Omaha.

STUDIES OF CRYOGLOBULINS: II. THE SPONTANEOUS PRECIPITATION OF PROTEIN FROM SERUM AT 5° C. IN VARIOUS DISEASE STATES. AARON BUNSEN LERNER, CYRUS P. BARNUM and CECIL J. WATSON, Am. J. M. Sc. **214**:416 (Oct.) 1947.

In a study of 121 serums from as many persons, having a variety of pathologic conditions, spontaneous precipitation of protein from the cooled serum was observed in 31 instances. The presence of these proteins, which are designated as cryoglobulins, may be regarded as a nonspecific indication of a disease process. They were not encountered in any of the serums from 40 normal persons.

Serums which contained cryoglobulins were divided arbitrarily into three grades on the basis of amounts. These are as follows: grade 1, from a trace to 6 mg.;

grade 2, from 6 to 25 mg., and grade 3, greater than 25 mg., per hundred cubic centimeters. Grade 3 cryoglobulinemia was encountered in but 1 case, and in this instance there is reason for the belief that the cryoglobulin was related to a severe purpura which stood in the foreground of the clinical picture.

HENSKE, Omaha.

THE CORONARY ARTERIES OF INFANTS. WILLIAM LOUIS MINKOWSKI, Am. J. M. Sc. **214**:623 (Dec.) 1947.

Coronary intimal thickenings may be expected to occur in a large number of newborn babies, infants and children who have died of various causes. In a group of 51 boys and 25 girls less than 1 day old, who died of birth trauma and/or asphyxia, the mean difference in thickness of the coronary intima between boys and girls was strongly suggestive, if not actually significant.

The role of acute infections appear to be important in producing intimal thickenings in older infants and children. The meaning of these intimal thickenings, particularly as concerns the subsequent development of coronary arteriosclerosis, remains to be clarified.

HENSKE, Omaha.

CONGESTIVE SPLENOMEGALY (BANTI'S SYNDROME) DUE TO PORTAL STENOSIS. DENNIS S. SHILLAM, California Med. **67**:379 (Dec.) 1947.

A review of the more important evidence for and against the existence of "Banti's disease" (congestive splenomegaly) leads to the conclusion that most, if not all, cases are based on portal obstruction with portal hypertension. A case of congestive splenomegaly in a 4 year old child due to congenital stenosis of the portal vein is presented with the observations at autopsy.

PRYOR, Redwood City, Calif.

CARDIAC DISEASE IN HELLENIC NURSERIES OF LUEKOSIA, CYPRUS. KYPROS CHRYSANTHIS, Arch. M. Knowl. (Aug. 10) 1946.

The results of this investigation of cardiac disease in nurseries are as follows:

1. The incidence of cardiac diseases among pupils is between 3 and 3.4 per cent.

2. The incidence of rheumatic heart diseases is between 0.7 and 1.5 per cent, while the incidence of congenital heart diseases is between 1.2 and 1.8 per cent.

3. It is important that the school medical officers examine the hearts of pupils with special attention because a number of conditions remain undiagnosed because of various reasons.

4. It is necessary that the teachers know something of the complications of rheumatic fever in order to advise the patient to see a physician as early as possible, so as to avoid further cardiac complications.

FROM THE AUTHOR'S SUMMARY.

EXPERIENCES WITH THE BLALOCK OPERATION FOR TETRALOGY OF FALLOT. F. D. DODRILL, Arch. Surg. **55**:539 (Nov.) 1947.

The author reports on 13 operations. For all patients the diagnosis was confirmed by the observation of a small, pulseless, or nearly pulseless, pulmonary artery. Three of the patients died after the operation; an excellent result was obtained in 5; no change in symptoms was noted in 2 persons; a good result was

obtained in 1 and a fair result in 1, and 1 operation was too recent to determine the result. The cause of death in 3 patients was shock, cardiac insufficiency and pulmonary hemorrhage.

KAISER, Rochester, N. Y.

THE EFFECT OF NIKETHAMIDE ON CORONARY BLOOD FLOW AND CARDIAC OXYGEN METABOLISM. JAMES E. ECKENHOFF and JOSEPH H. HAFKENSCHIEL, J. Pharmacol. & Exper. Therap. **91**:362 (Dec.) 1947.

Anyone who has observed the administration of nikethamide (coramine®) as a "last resort" to infants or children by house medical officers will agree with the authors' final conclusion. For this reason the following points from their excellent summary are presented:

In anesthetized, spontaneously breathing, heparinized dogs, the effects of nikethamide, papaverine, aminophylline, amyl nitrite and glyceryl trinitrate on coronary blood flow were measured by the bubble flowmeter. In order of their effectiveness these drugs could be listed as follows: papaverine, aminophylline, amyl nitrite, glyceryl trinitrate and nikethamide.

An approach necessary for the proper evaluation of the effect of a drug on coronary blood flow was presented. This approach attempted to correlate (*a*) the ratio between the oxygen supplied to the myocardium and the oxygen demanded by the myocardium (nutritional index) and (*b*) the efficiency of the muscle cells in making the energy transformations necessary to accomplish the work loads imposed on the heart. With the use of this approach, nikethamide when injected in large amounts was observed to increase coronary blood flow but at the expense of a decreased mechanical efficiency.

In experiments on 6 unanesthetized dogs, nikethamide in amounts necessary to produce an increase in coronary blood flow produced convulsions in 1 dog and undesirable symptoms in the others. Repetition of the same, or a decreased, dose in 3 animals produced convulsions and delayed death.

These authors' investigations gave them no indication of the reason nikethamide should enjoy such widespread clinical use in the treatment of cardiovascular disease.

PILCHER, Cleveland.

HYPOPROTEINEMIA AND PLASMA TRANSFUSION. OTTO SAXL and ANTONÍN VYKYDAL, Pediat. listy **2**:144, 1947.

After the experiences of two world wars, the administration of plasma has become an inevitable part of therapy. Good results are obtained especially in the following diseases: nephrosis, nephritis with hypoproteinemia and with renal edema, preeclampsia, parenchymatous damage to the liver, violent and protracted diarrhea, infections (i.e., cholera, dysentery and typhus), cachexia, inanition, gangrene, anemia and avitaminoses.

As human plasma is hard to obtain in sufficient amounts and is expensive, attempts were made to replace it. According to Masson (in Hungary, Melka, Karpant and Zapletal), denatured calf plasma seems to be the best substitute. For the estimation of the necessary amount of blood, plasma, isotonic sodium chloride solution and glucose in the treatment of the aforementioned conditions the method of Phillips and Van Slyke is suitable. It is simple and enables the simultaneous estimation of protein level, hemoglobin concentration and the hematocrit reading.

This paper deals with the performance of the method by estimation of the specific gravity of the blood and plasma in solutions of magnesium sulfate of different specific weights. The results obtained in 75 estimations are briefly recorded. On grounds of the results the authors speculate on the pathogenesis

of nephrosis, in which, at least sometimes, the changes in the kidneys are considered to be secondary. The changes in those forms of nephrosis and the changes in all organs in alimentary toxicosis and other diarrheal diseases are considered to be due to hypoproteinemia. The hypoproteinemia might be caused by the action of H substance (histamine) on the capillary vessels.

FROM THE AUTHORS' SUMMARY.

Diseases of Nose, Throat and Ear

ACUTE LARYNGOTRACHEOBRONCHITIS. F. W. DAVISON, Arch. Otolaryng. **47**:455 (April) 1948.

The decreasing mortality from laryngotracheobronchitis is discussed and 52 consecutive cases without a death, including 15 tracheotomies, are reported. However, case histories are not presented and the criteria for diagnosis and indications for tracheotomy are indefinite. Humidified oxygen, penicillin, postural drainage and early tracheotomy are the recommended treatments.

KIMBALL, Evanston, Ill.

THE PARENT'S ROLE IN THE CLINICAL PROGRAM. KENNETH SCOTT WOOD, J. Speech & Hearing Disorders **13**:209 (Sept.) 1948.

The speech clinician must bring about a revision of the parents' attitudes toward the cause of the child's speech defect. Parental frame of reference must be broken down and cooperation in discovering and alleviating family problems must be brought about. Parents should have a program of self analysis gained by reading especially assigned texts in this area. Parents should be required to report on clinical success at home.

PALMER, Wichita, Kan.

DIAGNOSIS AND PROGNOSIS IN CLEFT PALATE SPEECH. CLAUDE E. KANTNER, J. Speech & Hearing Disorders **13**:211 (Sept.) 1948.

Nasality at present is still a subjective phenomenon. The amount of nasality does not seem to be directly related to the amount of air escaping through the nose or the degree of opening of the soft palate. Nasality in cases of cleft palate cannot be dealt with intelligently on the basis of an assumption that it is simply a matter of undergoing repair of the soft palate and then learning to use it. Devices for showing nasality may be valuable in teaching, but they are not valuable or reliable as detectors of nasality. It is necessary to observe the speech patterns, the speech organs and the case history in order to predict a proper series of technics. An outline of the proper procedure in diagnosis is presented. The goal for every person with cleft palate should be to make available to him the best possible speech training commensurate with his needs, physical limitations, mental ability and potential contribution to society. The author is of the opinion that physicians and surgeons are both farther along toward this goal than are speech clinicians.

PALMER, Wichita, Kan.

INFANT SPEECH: THE EFFECT OF FAMILY OCCUPATIONAL STATUS AND OF AGE ON USE OF SOUND TYPES. ORVIS C. IRWIN, J. Speech & Hearing Disorders **13**:224 (Sept.) 1948.

Data on speech sounds collected on two groups of infants, one including children from homes of laboring families, the other from homes of business, clerical and professional persons, were analyzed in terms of phoneme type. The mastery of speech sounds for the two groups was found to proceed at different rates. The

equation for development of phoneme type of the babies in working class homes is $P_1 = 8.3\ A^{0.410}$, while that for the other group is $P_1 = 7.8\ A^{0.497}$. Analyses of variance yield F ratios indicating significant differences between the two groups, especially for occupational status during the last year of infancy.

PALMER, Wichita, Kan.

AN ANALYSIS OF WOOD'S ARTICULATION INDEX. ERNEST H. HENRIKSON, J. Speech & Hearing Disorders **13**:233 (Sept.) 1948.

The speech of 3 individual children and two groups of 12 and 14 children each, with mean ages of 8 and 13 years, was recorded. This was too small a group, but, as a result of study on the frequency of occurrence of each sound position, the conclusions were as follows: First, the rank order of frequency of occurrence of consonant sounds in children's speech presented by Travis corresponds approximately with the order of occurrence found in this study. Second, prorating consonant sounds on the assumption that they occur equally or approximately equally in a word is not justified. Third, the use of such proration as the basis for constructing an index of progress is not justified, and the value of conclusions drawn from the use of such an index is correspondingly questionable.

PALMER, Wichita, Kan.

EVALUATING THE EFFICIENCY OF GROUP SCREENING TESTS OF HEARING. HAYES A. NEWBY, J. Speech & Hearing Disorders **13**:236 (Sept.) 1948.

This is a description of a simple technic which can be applied to study the efficiency of a group screening test. In examining the efficiency of a group pure tone screening test, every fourth child was tested individually. The more subjects tested individually, the better was the measure of efficiency obtained. No fewer than 50 subjects, or 100 ears, should be tested individually in any group. The writer found it useful to combine pupils of the eighth and seventh grades, the sixth, fifth and fourth grades and the third and second grades in a sampling test of group screening in the school system. A convenient method of graphically examining the data thus obtained is the use of a tetrachoric table. This method is not used to obtain a coefficient of correlation but merely to portray the data in a meaningful fashion. Once a criterion of significant hearing loss has been properly established, it is an easy matter to adjust the efficiency of any group test by means of a tetrachoric table. If no amount of juggling of the criterion of significance of the group test results in reducing the percentage in any particular cell used to indicate success without raising the percentage in another cell used to indicate failure, then the group test is not operating with satisfactory efficiency.

PALMER, Wichita, Kan.

CO-OPERATION IN A PUBLIC SCHOOL SPEECH CORRECTION PROGRAM. THOMAS D. HOUCHIN, J. Speech & Hearing Disorders **13**:247 (Sept.) 1948.

The place of the speech correctionist in the public school system is reviewed, with advice to the beginning speech correctionist on ways in which to fit into the public school program.

PALMER, Wichita, Kan.

A PUBLIC SCHOOL PROGRAM FOR HARD OF HEARING CHILDREN. ELVENA MILLER, J. Speech & Hearing Disorders **13**:256 (Sept.) 1948.

This article presents a description of public school work with children with losses in hearing.

PALMER, Wichita, Kan.

ANTICIPATORY SPEECH RESPONSES IN CHILDREN WITH ARTICULATORY DEFECTS. MARY ELLEN HULL, J. Speech & Hearing Disorders **13**:268 (Sept.) 1948.

Thirty-two public school children, varying in age from 5 to 12 years, with articulatory defects were compared with 14 normal controls of the same age and general intelligence. A series of tests of repetition of vowels or nonsense syllables and words was given individually to each child in an effort to describe a phenomenon observed at the Institute of Logopedics, known as the anticipatory response. In children with articulatory defects production of each syllable was altered to a much greater extent when repeated in an anticipatory manner than when there was a delay between the stimulus sound and the speech response. The anticipatory speech response is not limited to children with articulatory defects. One child was nervous, distractible and below average intelligence who made such responses. Any child with an articulatory defect who had anticipatory reactions of sound could be taught to inhibit these reactions. The anticipatory speech response is defined as that type of response in which the child has an overrapid sound reaction in speech to the stimulus of a nonsense syllable by the examiner and the reaction by the child is made apparently without conscious study of production. In the normal and in the articulatory-defective person, the usual response is produced with a considerable delay between the utterance of the syllable by the examiner and the response by the child.

PALMER, Wichita, Kan.

INFANT SPEECH: THE EFFECT OF FAMILY OCCUPATIONAL STATUS AND OF AGE ON SOUND FREQUENCY. ORVIS C. IRWIN. J. Speech and Hearing Disorders **13**:320 (Dec.) 1948.

Data on speech sounds were collected on two groups of infants, one composed of babies from homes of business, clerical and professional persons and the other of infants from homes of laboring families, and analyzed on the basis of phoneme frequency. The development of the two groups proceeded at different rates. The equation for phoneme frequency of infants from nonlaboring families is $P_F = 59\ e^{0.0633\ A}$ and that for infants in workers' homes is $P_W = 63\ e^{0.0424\ A}$. There are significant differences when compared by F ratios. The occupational component is negligible during the first one and one-half years of infancy but during the last year it is highly significant.

Diseases of Lungs, Pleura and Mediastinum

SPIROMETRIC EVALUATION OF "ETHYL-NOR-EPINEPHRINE" IN BRONCHIAL ASTHMA. LOUIS LEVY and JOHN H. SEABURY, J. Allergy **19**:58 (Jan.) 1948.

Spirometric studies were performed on 10 patients with moderately acute attacks of asthma prior to and following the administration of 2 mg. of ethyl-nor-epinephrine (butanefrine,® 1-[3,4-dihydroxyphenyl]-2-amino 1-butanol hydrochloride). Eight of the 10 patients obtained symptomatic and objective relief, as evidenced by an increase of vital capacity, reserve air, complemental air and expiratory differential. There was an absence of side effects from the drug. Two patients required additional medication.

HOYER, Cincinnati.

BRONCHIAL ASTHMA IN INFANTS AND CHILDREN—ITS DIAGNOSIS AND TREATMENT. ALBERT H. ROWE and ALBERT ROWE JR., California Med. **69**:261 (Oct.) 1948.

The studies of these authors show that bronchial asthma in early and late childhood is practically always caused by food or inhalants and rarely by drugs or bacteria.

They explain recurrent attacks by the gradual accumulation of reacting bodies in the cells of the lungs. Between attacks they often observed relief, except for some symptoms, between 2 and 5 a. m. When relief was complete during summer months, the commonest cause of perennial asthma and/or "head colds" was food allergy.

Skin tests frequently give negative results to foods causing cumulative or chronic symptoms and thereby may fail to reveal clinical food allergy. Elimination diets, especially cereal-free diets, are recommended in the control of food allergy. Environmental control and desensitization with inhalant allergens that cannot be avoided are recommended for control of inhalant allergy. Bacterial allergy was found rarely as the cause of bronchial manifestations. The specific and symptomatic treatment of chronic and intractable bronchial asthma is outlined.

PRYOR, Redwood City, Calif.

STAPHYLOCOCCAL PNEUMONIA WITH OBSTRUCTIVE EMPHYSEMA. DONALD PATERSON, Proc. Roy. Soc. Med. **40**:165 (Feb.) 1947.

The patient, a boy 3 weeks of age, was admitted to the hospital with a temperature of 102 F. and rales over all the right side of the chest. There was a small submandibular abscess discharging. This abscess on the chin had been opened one day before his admission to the hospital. Culture of the blood and swabs from the throat, umbilicus and the boil on the chin grew coagulase-positive Staphylococcus aureus. A roentgenogram of the chest showed collapse and consolidation in the upper lobe of the right lung. The baby became very ill and cyanosed, and a roentgenogram taken a few days later showed an opacity in the lower lobe of the right lung. The mediastinum became greatly displaced toward the left by the obstructive emphysematous condition on the right side; 15 to 20 cc. of air was removed, which gave a little relief of the mediastinal displacement. Later, the mediastinum was found to be approximately central again. A week later the child was discharged from the hospital gaining weight slowly. The treatment used is given fully in the conclusion of the report.

WILLIAMSON, New Orleans.

STRATIGRAPHIC STUDY OF THE MEDIASTINUM IN CHILDREN. GIULIO DE GIULI, Riv. clin. pediat. **45**:500 (Aug.) 1947.

The author describes the normal stratigraphic appearance of the mediastinum in children, as revealed from the study of healthy children. Attention is drawn to the differences from the structure as observed in adults. The prominence of one shadow, which may be that of the left auricle of the heart, seems to be of particular interest.

FROM THE AUTHOR'S SUMMARY.

BRONCHIECTASIS IN A SIX YEAR OLD BOY WITH LOBECTOMY. J. M. PELLIZA and J. E. MOSQUERA, Arch. argent. de pediat. **27**:136 (March) 1947.

This is a report of a case of severely complicated bronchiectasis of the lower lobe of the left lung. Lobectomy was successfully performed. The pathologic report was lobular bronchiectasis.

ROJAS, Boston.

PULMONARY OIL EMBOLISM. S. GONZALEZ AGUIRRE and E. P. DE DIAZ, Arch. argent. de pediat. **27**:605, 1947.

A pulmonary antiseptic in an oil base was injected accidentally into a vein of a 7 year old boy. The main symptoms observed were dyspnea, cyanosis, cough, vomiting and foamy and bloody sputum. The patient recovered after the first twenty-four hours.

ROJAS, Boston.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

PRIMARY HEMANGIOENDOTHELIOMA OF THE LIVER IN INFANCY. S. W. BEREZIN, J. G. SHARNOFF and J. D. STEIN, New England J. Med. **238**:906 (June 24) 1948.

The authors add the case of primary hemangioendothelioma of the liver in infancy in the youngest child yet observed to the 19 known cases. They describe the characteristic abdominal enlargement, which is progressive and may be accompanied with constipation, abnormal stools, vomiting, pain and loss of weight. This tumor is a malignant one, in both histologic and clinical characteristics, and results in death.

GENGENBACH, Denver.

HYPOEVOLUTISM IN CHRONIC DISEASES OF THE DIGESTIVE TRACT. IGNAZIO GATTO, Riv. clin. pediat. **46**:145 (March) 1948.

Four patients with chronic diseases of the digestive apparatus (esophageal spasm, celiac disease and congenital megacolon) were examined, and a hypoevolutism of average severity, consisting in a reduction of size ranging from 12 to 16 per cent, was observed. The small bodily proportions proved the condition to be of an infantile type.

In most cases it must be inferred that the hypoevolutism was the consequence of chronic disease of the digestive apparatus and that the cause of the evolutional deficiency was the state of chronic hyponutrition and, particularly, the persistent hypovitaminosis and acidosis.

FROM THE AUTHOR'S SUMMARY.

GLYCOGENOLYTIC POWER OF PAROTID SECRETION IN CHILDREN. GINO CARDINI, Riv. clin. pediat. **46**:343 (June) 1948.

In order to investigate the activity of the parotid gland in regard to the production and regulation of diastase in the organism, 101 normal children were studied with the methods of Ottenstein and Wohlgemuth.

This study is new because researches on parotid secretion taken directly from Stensen's duct by a method which guarantees a sufficient exactitude of results are lacking, at least so far as the author knew, in adults and certainly in children.

As the method is based on the splitting of glycogen, the author preferred to use the name "glycogenolytic power" rather than "diastase activity."

Along with the parotid secretion, he made determination on the saliva and the blood serum. The average values obtained were, respectively, 5,058, 4,840 and 272 micrograms per hundred cubic centimeters. The individual variations were wide, especially in the blood serum. Between the saliva and the parotid secretion a certain parallelism was in evidence, but no close relation was observed between the parotid secretion and the blood serum. However, only normal children were studied and from these he could not determine whether the extreme variations might correspond to proportional alterations. It will be possible to observe this by experiment or in pathologic cases; for this purpose, he is making experimental and clinical studies.

In any case, he seems to have done a useful work in establishing the average rates of the glycogenolytic power of the parotid secretion, its variations and its relation to the blood serum and saliva in the normal child, giving in this way the basis for further studies on this interesting subject.

FROM THE AUTHOR'S SUMMARY.

Nervous Diseases

ROLE OF "AGENIZED" FLOUR IN THE PRODUCTION OF RUNNING FITS. G. W. NEWELL, T. C. ERICKSON, W. E. GILSON, S. N. GERSHOFF and C. A. ELVEHJEM, J. A. M. A. **135**:760 (Nov. 22) 1947.

Running fits were produced in dogs fed high levels of flours bleached with nitrogen trichloride or flours bleached with combinations of nitrogen trichloride and benzoyl peroxide. Fits did not appear in dogs fed untreated flours or flours treated with benzoyl peroxide, chlorine dioxide, chlorine, nitrogen dioxide or methyl dichloramine. Studies on the blood of dogs which had fits showed no abnormalities.

Fractionation of wheat flour and wheat gluten has shown that the toxic factor is associated with the protein of wheat but not with the lipid or carbohydrate.

Monkeys fed highly "agenized" whole wheat flour rations showed some changes in the electroencephalographic patterns but did not show any of the clinical symptoms associated with running fits. Nitrogen trichloride–treated wheat products had no adverse effect on rats, chicks or guinea pigs. Growth responses of rats and chicks fed nitrogen trichloride–treated whole wheat flour and unbleached whole wheat flour were the same. Convulsive seizures have been produced in cats fed "agenized" flour.

In preliminary studies, human subjects have been fed "agenized" wheat products for two to four weeks. No changes in the electroencephalographic patterns were obtained, nor were any abnormal clinical symptoms noted.

FROM THE AUTHORS' SUMMARY.

SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD OCCURRING IN IDENTICAL TWINS. GABRIEL A. SCHWARZ and JOHN C. TODD, Am. J. M. Sc. **214**:94 (July) 1947.

Clinical and laboratory findings on identical twins, with subacute combined degeneration of the spinal cord, gastric achlorhydria and recovery with liver therapy, are reported. The monozygosity of the brothers was established on the basis of identical physical characteristics, blood groups and finger and palm prints.

These cases, in the authors' opinion, strengthen the concept of heredity as one of the etiologic factors in the development of posterolateral sclerosis.

HENSKE, Omaha.

DEGENERATION AND NECROSIS OF NEURONES IN EIGHTH CRANIAL NUCLEI CAUSED BY STREPTOMYCIN. LEWIS D. STEVENSON, ELLSWORTH C. ALVORD JR. and JAMES W. CORRELL, Proc. Soc. Exper. Biol. & Med. **65**:86 (May) 1947.

Neuropathologic study was made on 5 patients with tuberculosis who had acquired partial or complete deafness while receiving large amounts of streptomycin. Changes were present in the neurons of the ventral cochlear nuclei in all of them. Streptomycin in comparable dosage was administered to 3 dogs, which showed ataxia, tail chasing, weaving of the head and weakness, but disturbance in auditory acuity could not be demonstrated. Liquefaction necrosis was found bilaterally in the ventral cochlear nuclei; hence the changes would seem to account for the deafness and vestibular dysfunction in clinical cases.

HANSEN, Galveston, Texas.

EFFECT OF WHEAT GLUTEN DIET ON THE ELECTROENCEPHALOGRAMS OF DOGS. G. W. NEWELL, T. C. ERICKSON, W. E. GILSON and C. A. ELVEHJEM, Proc. Soc. Exper. Biol. & Med. **65**:115 (May) 1947.

Electroencephalographic tracings were made on 18 puppies 6 to 8 weeks of age which were maintained on a diet of casein, sucrose, salt mixture, corn oil, whole liver powder and vitamin supplements. When wheat gluten was substituted for casein, the animal had "running fits" (J. R. Wagner and C. A. Elvehjem.: *J. Nutrition* **28**:431 [Dec.] 1944). From three to twenty-four days after the change in the diet, electroencephalographic tracings characteristic of those seen in human subjects with epilepsy were noted. In several instances the tracings were again observed to be normal and the animals behaved as usual when casein replaced the substituted wheat gluten. Data on 1 representative animal are presented.

HANSEN, Galveston, Texas.

A STUDY OF ENCEPHALITIS. MILDRED GOTTDANK and DORIS TREPEL, Quart. J. Speech **33**:355 (Oct.) 1947.

A review of the medical background of encephalitis and the report of a patient with an ambulatory chronic type worked with in the speech clinic for eighteen months are given. Symptoms in a postencephalitic adult coming to the speech clinic will be a combination of one or more of the following signs: tremors, drooling, a masklike expression, bizarre posture and definite speech difficulties. A person with chronic encephalitis finds himself burdened with physical, social, vocational and economic problems to which are added, for the most part, the additional burden of voice and articulatory difficulties.

The patient described showed a tremor of the left arm, masklike expression, infrequent blinking, stooped posture and uneven gait. The voice was monotonous, lacking variation in pitch and rate and almost inaudible. The rhythm was irregular, and the patient seemed to find difficulty in verbalizing his thoughts. There was apparently poor lip and lingual mobility which made articulation sluggish, although there was good control of lingual and labial muscles. The breathing was somewhat shallow, and the entire speech pattern lacked animation. The patient appeared frightened during the interview, and it was impossible to put him at ease. The patient stated he had always needed speech training but had never had the courage to go to a clinic for help.

Technics used consisted in practice of reading exercises, the use of the voice mirror and development of good phonation. When phonation became habitual, lip and tongue exercises were begun with encouragement to the patient to articulate clearly individual sounds and, later, words, phrases and sentences. After this, work with pitch, rate and intonation was begun. Question and answer practice was carried out for many weeks. Finally, the subject was placed before a mirror and many facial expressions were tried out and used. When the patient was discharged, emotional and psychologic integration was at least well on its way to successful completion. On discharge he was able to speak of his difficulty with ease and objectivity and was free from destructive self consciousness. He still had a fixed expression to some extent, occasional thought difficulties and, during fatigue, lip immobility. Both clinic and patient were satisfied with the results. It seems reasonable to believe that there are many other ambulatory chronic encephalitic patients who could benefit by speech reeducation.

PALMER, Wichita, Kan.

CEREBROSPINAL MENINGITIS WITH FLACCID NECK AND VENTRICULAR COLLAPSE. R. DEBRÉ, S. THIEFFRY and A. DOUMIC, Pédiatrie **36**:5 (Jan.-Feb.) 1947.

The authors describe a picture of epidemic meningitis, characterized by an absence of stiffness of neck and back muscles, absence of the Kernig sign and, in small infants, a sunken fontanel and overriding sutures. The flaccidity of neck muscles makes the differential diagnosis from other diseases, e.g., poliomyelitis, difficult.

The 7 patients observed by the authors ranged from 5 months to 4½ years of age. The onset of the disease was as expected in meningitis. The disease responded to treatment with sulfonamide compounds and penicillin, and clinical and laboratory findings improved. Suddenly, the patients' conditions took a turn for the worse, although some of the patients showed the severest signs from the onset. The following signs were observed: fever, stupor and coma, dehydration, flaccidity of neck and back and absence of the Kernig sign. If untreated, these children soon died in coma.

As causative factors are listed toxemia of infancy, encephalitis or disturbance of circulation and absorption of the spinal fluid, with hypotension of the cerebral fluid and collapse of the ventricles. The last two symptoms were proved surgically in 1 case studied by the authors. Therapeutically, the authors suggest in such patients the heroic treatment of trepanation and injection of saline solution or air into the ventricles. In infants the open fontanel can be used for injection. They also cite good results with much less radical methods, such as hydration of the entire patient by continuous intravenous infusion. This last method is recommended. Direct injection into the ventricle is reserved for the most seriously ill patients who do not respond to the general hydration therapy.

GLASER, Chicago.

Psychology and Psychiatry

MENTAL DEFICIENCY OF PRENATAL ORIGIN: A CHALLENGE TO PREVENTIVE MEDICINE. PETER GRUENWALD, Am. J. M. Sc. **214**:605 (Dec.) 1947.

This brief review shows that there is hardly one field in medicine which cannot contribute information needed for the prevention of mental deficiency, blindness and deaf-mutism. Just how many cases are due to each of the aforementioned factors may not be known until they can be prevented. In view of the information now at the physician's command, he can no longer say that antenatal causes of mental deficiency are beyond medical control. The cost of the most extravagant research program in this field may turn out to be less than the savings of communities resulting from a reduced number of inmates in their institutions.

HENSKE, Omaha.

THE IMPACT OF MODERN PSYCHIATRY ON MEDICAL EDUCATION, MEDICAL PRACTICE AND HOSPITAL ORGANIZATION. LAWRENCE S. KUBIE, Bull. Johns Hopkins Hosp. **80**:348 (June) 1947.

The author reviews the changes in psychiatric practice in the last twenty-five years. For a primary preoccupation with the psychoses it has substituted a primary preoccupation with the neuroses.

He considers the neurotic process to be actually and in reality universal, that it can and does coexist with every other medical and surgical ill to which human beings are heir, and that it is often masked.

Concerning preventive psychiatry, he states that

"That which can be done in the nursery or in the community to prevent neuroses requires a population which is emotionally more mature, better instructed, more informed, and freer from bias and bigotry than exists. Taking the world as it is today, prevention means primarily one thing: to treat every flurry of psychiatric symptoms as a medical emergency. This means early treatment of every transitory neurotic episode of childhood." But another step in prevention would be a psychiatric appraisal early in the examination of every patient.

The vast number of men trained in psychiatric technics can be obtained, the author suggests, if the medical schools and teaching hospitals develop a new paramedical specialty with a doctorate in medical psychology. The training would include clinical apprenticeships in general and in psychiatric hospitals.

LYTTLE, Los Angeles.

AN APPRAISAL OF SOME PSYCHOLOGICAL FACTORS IN RELATION TO ROOMING-IN AND SELF-DEMAND SCHEDULES. SIBYLLE K. ESCALONA, in Senn, M. J. E.; Problems of Early Infancy, Transactions of the First Conference, March 3-4, 1947, New York.

Present knowledge of the psychology of infancy supports the idea that close contact between mother and child during the lying-in period is desirable. Probably this method should not be used except with healthy, well adjusted mothers.

MCGUIGAN, Evanston, Ill.

PARENT CHILD RELATIONSHIP AND CHILD'S SELF-REGARDING SENTIMENT. JNANENDRA DASGUPTA, Indian J. Pediat. **14**:65 (April) 1947.

One hundred and thirty-seven children, averaging 12 years of age, were questioned regarding their feelings toward their parents and themselves. The answers suggest that the child who hates his parents hates himself also. Children who are loved by both parents feel themselves to be good. The reverse is also true. A child's belief in his own goodness is a valuable thing. Belief in his own badness is probably a major factor in delinquency.

MCGUIGAN, Evanston, Ill.

CHILDHOOD DEMENTIAS. R. REY ARDID, Rev. españ. de pediat. **3**:141 (March-April) 1947.

This article is an exhaustive review of the literature on the dementias of childhood. The first part of the article, on the subject of juvenile dementia paralytica, is reasonably lucid and interesting. The discussion of dementia precox, the infantile dementia of Heller and the simple dementias is not so clear, and the final chapter on dementias secondary to diverse infectious abiotrophic and toxic processes is confusing to the average reader. There is no original material in the article, and, in the abstracter's opinion, the subject is not one which lends itself to condensations of this type.

MILLER, Newark, Ohio.

Diseases of the Genitourinary Tract

METABOLIC EFFECTS OF RENAL INSUFFICIENCY IN CHILDREN. FRANCIS SCOTT SMYTH, California Med. **70**:23 (Jan.) 1949.

Chronic renal disease in children is frequently associated with stunting of growth or dwarfing. The bones in many of these patients lose their essential

minerals—calcium and phosphorus. Diets which are alkaline, high in calcium and low in phosphorus are of value in preventing the bone defect. Administration of aluminum hydroxide by mouth may have a similar beneficial effect. Underlying both the dwarfing and the faulty bone development may be loss of calcium or phosphorus or interference with the body's use of hormones and vitamins.

PRYOR, Redwood City, Calif.

INFLUENCE OF THE DIET UPON THE NEPHROSCLEROSIS, PERIARTERITIS NODOSA AND CARDIAC LESIONS PRODUCD BY THE "ENDOCRINE KIDNEY." HANS SELYE and HELEN STONE, Endocrinology **43**:21 (July) 1948.

Experiments on the rat indicate that the production by the "endocrine kidney" technic of hypertension and its morphologic accompaniments (nephrosclerosis, cardiac hypertrophy, myocarditis, periarteritis nodosa) remains uninfluenced by the protein and sodium chloride concentration of the diet. These observations are contrasted with those of the extreme dependence on sodium for the production of the same lesions by desoxycorticosterone or extracts from the anterior lobe of the pituitary. It is concluded that protein increases the corticotropic action and that sodium augments the effects of mineralocorticoids.

JACOBSEN, Buffalo.

METHEMOGLOBINEMIA IN YOUNG INFANTS. M. CORNBLATH and A. F. HARTMANN, J. Pediat. **33**:421 (Oct.) 1948.

The ingestion of well water containing nitrate by small infants and reduction of the nitrate to nitrite by intestinal bacteria lead frequently to methemoglobinuria. In the authors' experience infants with this condition did not have free gastric acidity, and the p_H of the gastric secretions was greater than 4. Although the authors were able to demonstrate that lactic acid in a concentration of 0.5 to 1 per cent prevented the development of methemoglobinemia, they endorsed the treatment of clinical patients with 1 to 2 mg. per kilogram of body weight of methylthionine chloride intravenously. Their bacteriologic studies revealed that organisms found in their patients which were capable of reducing nitrate to nitrite would not grow at p_H 4.

C. G. GRULEE JR., Galveston, Texas.

DIURETIC ACTION OF FORMOGUANAMINE IN NORMAL PERSONS. WERNER L. LIPSCHITZ and EDGAR STOKEY, J. Pharmacol. & Exper. Therap. **92**:131, 1948.

After preliminary experiments with dogs and rabbits showing that formoguanamine (diaminotriazine) was many times more effective as a diuretic than urea and that it seemingly was harmless as shown by the results of experiments and by observations of autopsies on the animals, its action on 8 healthy men was studied. Doses of 8 to 9 mg. of the drug per kilogram of body weight removed 90 to 100 per cent of ingested saline solution. Doses above 9 mg. per kilogram of body weight may produce thirst, prolonged diuresis and a feeling of discomfort in the lumbar region.

PILCHER, Cleveland.

GIANT OVARIAN CYST IN A NEWBORN INFANT. WILLIAM I. NEIKIRK and HENRY W. HUDSON JR., New England J. Med. **239**:468 (Sept. 23) 1948.

This report of the successful removal of a follicular cyst of the ovary and fallopian tube in a 34 hour old infant brings the reported total of such operations in the newborn period to 2 and emphasizes the rarity of the condition. In both instances abdominal distention and other symptoms and signs of intestinal obstruc-

tion were present, but it is clear that the correct preoperative diagnosis is difficult to make. A report of the histologic examination and assay of contents of the cyst is made.

WHEELOCK, Denver.

HEMOLYTIC STREPTOCOCCAL VAGINITIS IN CHILDREN. P. L. BOISVERT and DWAIN N. WALCHER, Pediatrics **2**:24 (July) 1948.

Hemolytic streptococcic vaginitis has been misdiagnosed as gonococcic vaginitis when only a direct smear of the discharge has been utilized for diagnostic purposes.

This study is based on the cultures taken on 286 patients seen at a pediatric inpatient service from 1925 through 1945 and in a pediatric clinic from 1935 through 1945. Five hundred and twenty-four vaginal cultures were examined. There were 37 patients (12.9 per cent) with hemolytic streptococci, 33 with gonococci and 11 with pneumococci.

Nasopharyngeal cultures were obtained from 30 of the 37 patients with hemolytic streptococcic vaginitis. Hemolytic streptococci were present in 17. These organisms were grouped in 13 instances, in every one of which they were observed to be of the same group as those found in the vagina.

The presenting complaints and chief symptomatology were referable to the vaginitis in 16 of the patients. In addition, hemolytic streptococcus vaginitis was seen associated with 4 cases of scarlet fever and with 1 each of streptococcic pharyngitis, streptococcic fever, impetigo, erysipelas of the genitalia, streptococcic peritonitis and streptococcic osteomyelitis.

The vaginal discharge was an acute symptom in the majority of the patients. The vaginal discharge and the physical findings were not sufficiently characteristic to be diagnostic with respect to the origin. Parenteral use of penicillin is considered the treatment of choice at present.

FROM THE AUTHORS' SUMMARY.

URINARY RETENTION DUE TO HEMATOCOLPOMETRA: REPORT OF TWO CASES—ONE WITH SPONTANEOUS RECOVERY. ALLAN BLOXSOM and NORBORNE POWELL, Pediatrics **2**:567 (Nov.) 1948.

Two cases of acute complete urinary retention due to hematocolpometra are reported. In 1 case there was spontaneous relief due to the fracture of the hymen when the patient sat up on the examining table. Seven previous cases are reported in the literature, in addition to the 2 described in this paper, and in 3 of the 9 cases some congenital intrinsic narrowing of the urethra is stated to have been present.

FROM THE AUTHORS' SUMMARY.

ABSORPTION OF PENICILLIN THROUGH THE HUMAN VAGINA. MELVIN SCHUDMAK and H. CLOSE HESSELTINE, Proc. Soc. Exper. Biol. & Med. **65**:15 (May) 1947.

Penicillin in vaginal suppositories, with a base of theobroma oil U. S. P., was given to 16 women, all but 1 of whom had trichomoniasis, without satisfactory results. Blood levels indicated that the rate of absorption of penicillin through the vaginal mucosa is unpredictable; hence only local conditions warrant this route of administration of penicillin.

HANSEN, Galveston, Texas.

AN UNUSUAL CONGENITAL DEFORMITY OF THE KIDNEY. R. F. POWELL, Canad. M. A. J. **60**:48 (Jan.) 1949.

An unusual case is reported of congenital malformation of the tubules and cyst formation of the parenchyma, with multiple branching of the tubular system.

McGUIGAN, Evanston, Ill.

TREATMENT OF ENURESIS AND ENCOPRESIS. BERNHARD BESKOW, Nord. med. (Hygiea) **31**:2102 (Sept. 13) 1946.

Eighty-three boys and 27 girls were treated for enuresis at the Göteborg Children's Hospital, Göteborg, Sweden; 94.6 per cent of the former and 81.5 per cent of the latter were discharged free from symptoms. Two years after their discharge, 26.6 and 21.7 per cent, respectively, of the children were still healthy; relapses had occurred in 28 and 26 per cent, and the rest were still being treated in their homes. Twenty-four boys and 6 girls had at the same time been treated for encopresis, and all except 1 was cured; this child had megasigmoid. The importance of following a careful regimen in the home after discharge from the hospital is stressed.

WALLGREN, Stockholm, Sweden.

Diseases of the Eye

WARREN TAY-SACHS DISEASE IN A CHINESE INFANT. G. HARIDAS, Brit. J. Ophth. **31**:428 (July) 1947.

A case of amaurotic family idiocy occurring in a Chinese Hylam male infant is reported, the first of its kind from Malaya. The child was 20 months 20 days old when he died. The diagnosis was based on the progressive muscular weakness, lack of mental development and blindness, with pathognomonic changes in the fundus.

The article is illustrated.

ZENTMAYER [Arch. Ophth.].

CONJUNCTIVAL NEVI. D. ARCURI, Rassegna ital. d'ottal. **15**:263, 1946.

The author discusses conjunctival nevi from a clinical standpoint by referring to the literature and by reporting 2 of his own cases. He stresses the importance of slit lamp examination, particularly with respect to the vascularization present. This examination may well be substituted for biopsy, which is technically more difficult and is not free from danger. The stationary nevus should be left undisturbed, while any nevus which increases in size should be freely excised surgically and followed by diathermy coagulation.

BIETTI—LO-PRESTI [Arch. Ophth.].

CONGENITAL SCLEROCORNEAL CYST: REPORT OF A CASE. V. BISCHLET, Ophthalmologica **114**:371 (Oct.-Nov.) 1947.

A case of congenital sclerocorneal cyst is reported. The article is well illustrated. The literature since 1853 is reviewed.

KIRBER [Arch. Ophth.].

Skin Diseases; Allergy

KAPOSI'S VARICELLIFORM ERUPTION: ISOLATION OF THE VIRUS OF HERPES SIMPLEX FROM THE CUTANEOUS LESIONS OF THREE ADULTS AND ONE INFANT. ISAAC RUCHMAN, ASHTON L. WELCH and KATHARINE DODD, Arch. Dermat. & Syph. **56**:846 (Dec.) 1947.

Four patients with Kaposi's varicelliform eruption are reported on, of which 1 was a 14 month old boy. There was a history of atopic dermatitis since the age of 1 month. The herpetic lesions lasted about forty-two days and were not affected by the administration of penicillin or sulfadiazine. From this child and the other 3 patients (aged 16, 23, 25 years), an agent was obtained from the lesions which was capable of producing keratoconjunctivitis in rabbits. All the patients

had had contact with persons having labial herpes from five to ten days previous to the onset of the eruption. The virus that was isolated was shown to be that of herpes simplex by histologic methods and cross immunity tests in animals.

CHINNOCK, Iowa City.

WARTS. H. J. TEMPLETON, California Med. **68**:23 (Jan.) 1948.

Warts are caused by a specific infection, viral in nature, and they are, therefore, contagious. The filtrate of warts curetted off and ground up will produce warts at the site of inoculation into the skin. The incubation period may be several months. Common warts on the glabrous skin are cured with greatest certainty by destructive measures. The author's personal preference is for electrodesiccation.

Plane, flat or juvenile warts seem to respond sometimes to the oral administration of potassium arsenite solution or protiodide of mercury. With such oral medication, one may combine daily painting of each flat wart with iodine tincture on a toothpick. Occasionally, if they occur in great numbers on the face, production of a mild peeling of the face with 10 to 15 per cent salicylic acid ointment applied once daily is the most practical treatment. Unfiltered roentgen therapy is also valuable.

In following any method of treatment for warts, one should remember that they are benign growths, that they are rarely harmful and that they may spontaneously disappear. Therefore, any treatment which might do the patient harm should be avoided.

PRYOR, Redwood City, Calif.

CONGENITAL DEFECT OF THE SCALP. H. MACKAY, Proc. Roy. Soc. Med. **40**:533 (July) 1947.

The patient, aged 4½ years, was an only child, small for his size. At birth there were four areas on the vertex where the skin was absent. They were covered with granulated tissue, and a systolic murmur was present. The ulcers healed well in about three weeks. Roentgenograms made at age of 1½ years showed the heart to be small and the long bones normal. When he was seen on examination, there were four areas of scar tissue with much keloid. The author was of the opinion the areas were developmental in origin because there was no evidence of intrauterine injury or amniotic adhesions.

WILLIAMSON, New Orleans.

ACRODYNIA. J. P. GARRAHAN and R. R. L. SAMPAYO, Arch. argent. de pediat. **26**:308 (Nov.) 1946.

The authors review the literature on acrodynia (erythredema polyneuropathy) and conclude that the lesions described are discrete, fail to be constant and have also been observed in pellagra and in pernicious anemia. They describe circulatory, neuropsychic and dermatologic syndromes found in this disease. They also review a group of additional symptoms, of the gastrointestinal tract, the respiratory system and the genitourinary tract, as well as ocular symptoms and osseous lesions.

Occasional coincidence of acrodynia with tuberculosis and rickets is pointed out.

ROJAS, Boston.

ACRODYNIA. J. P. GARRAHAN and R. R. L. SAMPAYO, Arch. argent. de pediat. **26**:383 (Dec.) 1946.

This article is the concluding portion of an extensive review of the literature on acrodynia (erythredema polyneuropathy), in which 61 recent references are given. The complications, causes of death, sequelae, diagnosis and treatment of the disease are taken up. The article also includes several case histories.

ROJAS, Boston.

AN ATTEMPT AT CLASSIFICATION OF THE INFANTILE DERMOPATHIES MORPHOLOGICALLY ECZEMATOUS. J. POU DIAZ, Rev. españ. de pediat. **3**:176 (March-April) 1947.

The author reviews the previous classifications of the eczemas. An excellent choice of cases is demonstrated in the photographs presented. The modesty of the author is notable in the presentation of his classification. The classification itself is, unfortunately, no great advance over the past ones. It is a great question whether classification is not an impossible task as long as the causation remains obscure.

MILLER, Newark, Ohio.

IMPORTANCE OF VITAMIN A IN DISEASES OF THE SKIN IN INFANTS. ALOIS PALACKÝ, Pediat. listy **2**:178, 1947.

On the basis of personal observations the author objects to the use of oxidizing agents (potassium permanganate and hydrogen peroxide, for example) in treatment of the skin in infants. According to him those substances locally destroy the vitamin A.

FROM THE AUTHOR'S SUMMARY.

SEVERE ALLERGY TO PHENOBARBITAL [LUMINAL] IN A CHILD. GUDMUND SPONLAND, Tidskr. f. d. norske lægefor. **66**:367 (June 1) 1946.

A girl 2½ years of age, who had previously been healthy and who had not displayed any allergic symptoms, was given 0.05 Gm. of phenobarbital (luminal) daily for one week and 0.15 Gm. daily for another week as treatment for nervousness. In all, she had received 0.55 Gm. of the drug, when she became ill with an allergic, maculopapular, partly vesicular exanthem, beginning on the face and rapidly spreading over all the skin. Her temperature was slightly elevated. No eosinophils were noted. Itching was severe. An oral exanthem with severe stomatitis made feeding difficult. Treatment with phenobarbital was immediately stopped. The manifestations disappeared within several weeeks.

WALLGREN, Stockholm, Sweden.

ALLERGY IN OXYURIASIS. SVEND HEINILD and HOLGER MADSEN, Ugesk. f. læger **108**:527 (May 30) 1946.

Results of intradermal tests with antigen from Enterobius vermicularis in 140 children, aged 2 to 14 years, are reported. A positive reaction was obtained in 31 per cent. The reaction was positive in 4 of 10 children with demonstrable ova and in 3 of 10 children without ova. Since there is no connection between the occurrence of Enterobius and the cutaneous reaction, it must be concluded that the reaction is not of allergic origin but must be considered as toxic. Seventy asthmatic patients showed a tendency to more intense reactivity than the other children. There is, however, a possibility of inhalation allergy to the ova of Enterobius vermicularis. The authors recommend testing allergic patients with positive reactions to house dust with Enterobius antigen.

WALLGREN, Stockholm, Sweden.

Surgery and Orthopedics

A STUDY OF BURNS AND SCALDS IN CHILDREN. BRENDA MORRISON, Arch. Dis. Childhood **22**:150 (Sept.) 1947.

Thirty-one cases of burns and scalds in children were studied. The main cause of illness and death in the early stages is reduction of blood volume by loss of plasma. Early and adequate replacement by transfusion is essential for recovery

in the type of case studied; therefore, the recognition, assessment and treatment of plasma loss is of prime importance during the first forty-eight hours.

The physical signs of reduced plasma volume are thirst, peripheral vasoconstriction, drowsiness, restlessness of spasmodic type and, eventually, mental confusion and loss of consciousness. These signs constitute a specific indication for intravenous therapy and must never be disregarded. Hypotension is a late sign, and treatment should never be delayed pending its appearance.

The hematocrit value is a more sensitive index of fluid loss and a better guide to treatment than the clinical state, though they should always be considered in conjunction. Calculations from hematologic data show that up to 30 per cent of the plasma volume may be lost from the circulation before clinical deterioration is obvious, and death probably occurs when 60 to 70 per cent of the plasma has been lost.

Certain "toxemic" signs may be seen during the second twenty-four hour period and in the succeeding weeks. Their nature is not understood, but they do not appear to be due to either fluid loss or secondary infection. They are sustained pyrexia and hyperventilation, moderate sustained hypertension and nervous signs suggesting increased intracranial pressure and due possibly to cerebral edema.

The problems of the recovery period are secondary infection and wasting, and they are interrelated. The maintenance of good morale during this period is of paramount importance, and the relief of anemia by blood transfusion and the avoidance of painful dressings are decidedly helpful in this respect. Sulfonamides are absorbed rapidly from the burned areas during the first two days, and care must be taken in their application.

Convulsions may be symptomatic of three conditions: circulatory inefficiency from untreated plasma loss; hypertension during plasma and serum reactions; the cerebral disturbance of the "toxic" phase.

KELLY, Milwaukee.

ASCORBIC ACID, THIAMINE, RIBOFLAVIN AND NICOTINIC ACID IN RELATION TO ACUTE BURNS IN MAN. C. C. LUND and OTHERS, Arch. Surg. **55**:557 (Nov.) 1947.

The study was undertaken to determine the alteration in the plasma concentration of ascorbic acid and in the urinary excretion of ascorbic acid, thiamine, riboflavin and N-methylnicotinamide in patients with burns admitted to the Boston City Hospital during 1944-1945.

The data obtained from careful studies indicated that large doses of these vitamins are needed by severely burned patients and that some supplementation at a lower level is needed for many patients with burns of moderate extent. A similar conclusion was reached in a study of patients with hemorrhagic shock, traumatic injuries and infection.

KAISER, Rochester, N. Y.

Miscellaneous

THE DISTRIBUTION OF DIHYDROSTREPTOMYCIN IN VARIOUS BODY FLUIDS. LOUIS LEVIN, DAVID T. CARR and FORDYCE R. HEILMAN, Am. Rev. Tuberc. **58**:531 (Nov.) 1948.

After the intramuscular administration of dihydrostreptomycin, the drug was rapidly absorbed into the blood, the greatest concentration being reached in about one hour. Significant quantities of the drug were present in the blood for twenty-four hours after the intramuscular administration of 1 or 2 Gm. The drug passed through the placental membrane and was detected in the fetal blood.

Dihydrostreptomycin was found in significant quantities in the pleural and cerebrospinal fluids of patients who had received the drug by intramuscular injection. The drug was excreted in large amounts in the urine, 70 per cent or more of the daily dose being present in each twenty-four hour sample. The absorption, distribution and excretion of streptomycin and of dihydrostreptomycin are similar.

Absence of symptoms of neurotoxicity after intramuscular administration of dihydrostreptomycin cannot be attributed to low concentration of the drug in the blood.

FROM THE AUTHORS' SUMMARY.

HYPERVOLEMIA IN MICE BEARING GRANULOSA CELL GROWTHS: TIME OF ONSET AND SOME ASSOCIATED PHYSIOLOGICAL AND CHEMICAL CHANGES. HARRY SOBEL and JACOB FURTH, Endocrinology **42**:436 (June) 1948.

It was noted recently that mice bearing subcutaneous growth of transplanted granulosa cells have enormously congested livers and adrenal glands and an associated hypervolemia with two or three times the normal values. The hypervolemia is present in mice bearing transplanted granulosa cell tumors originally induced by roentgen rays or produced by intrasplenic grafts of ovarian fragments into gonadectomized mice. It was suggeated that this increase in blood volume was produced, directly or indirectly, by a hypothetic substance elaborated by the neoplastic granulosa cell. The physiologic and chemical studies reported in this article were undertaken to learn more about the nature of this hypervolemia. Further work will be necessary to explain the phenomenon.

JACOBSEN, Buffalo.

THE USE OF PROCAINE HYDROCHLORIDE INTRAVENOUSLY IN THE TREATMENT OF REACTIONS TO PENICILLIN: REPORT OF FOUR CASES. ARMAND E. COHEN and JULIAN KAUFMAN, J. Allergy **19**:68 (Jan.) 1948.

Procaine hydrochloride was given intravenously to 4 patients who had a disease like serum sickness from sensitivity to penicillin. Two of them had a favorable response. The authors point out that serum sickness is a self-limited condition. The action of procaine hydrochloride is not clear. It should be kept in mind that some persons are sensitive to procaine hydrochloride and that unfavorable reactions may occur from its use. There are at present no known tests to determine sensitivity to the drug.

HOYER, Cincinnati.

CLINICAL EFFECTS OF EPINEPHRINE BY INHALATION: A SURVEY. ROBERT L. BENSON and FRANK PERLMAN, J. Allergy **19**:129 (March) 1948.

Oral inhalation of epinephrine in the treatment of asthma frequently gives relief. Relief diminishes with continued use of the drug, which results in more frequent use and the possibility of harm from overdosage. The authors studied 2,236 asthmatic persons seen over a period of ten years. These were mostly adults. Epinephrine was used orally by 648 of these patients. There were 48 deaths in this group, or 7.4 per cent. Twenty-two of 1,588 patients who did not use epinephrine orally died. This is a mortality rate of 1.4 per cent. Constant injudicious use of epinephrine produces pathologic changes in the entire respiratory tract which may well contribute to the death of the patient. This information was obtained from 48 autopsies. The observations were similar to those on experimental animals exposed to excessive amounts of epinephrine.

HOYER, Cincinnati.

THE TOXICITY OF FLOURS TREATED WITH VARIOUS "IMPROVING" AGENTS. JACK L. RADOMSKI, GEOFFREY WOODARD and ARNOLD J. LEHMAN, J. Nutrition **36**:15 (July) 1948.

Radomski and his co-workers raise the question whether the agene treatment acts by destroying a necessary dietary constituent of flour or by producing a toxic product. The fact in itself that the typical running fit syndrome can be produced in dogs on an acute basis strongly suggests that the problem is one of simple toxicity uncomplicated by dietary deficiencies. Although the data presented definitely demonstrated that the production of fright fits by the agene-treated gluten of flour is not a phenomenon peculiar to the dog but rather a toxic reaction common to several species, the question of possible toxicity to human beings is still unsettled. Obviously, a toxicant of such potentialities for harm is not a desirable constituent of the flour from which our daily bread is prepared.

FREDEEN, Kansas City, Mo.

POTASSIUM INTOXICATION: REPORT OF AN INFANT SURVIVING A SERUM POTASSIUM LEVEL OF 12.27 MILLIMOLS PER LITER. CLIFTON D. GOVAN JR. and WARREN M. WEISETH, J. Pediat. **28**:550 (May) 1946.

Recent studies have demonstrated the value of the use of potassium salts in the treatment of dehydration resulting from diarrhea. The therapeutic use of potassium is without danger, provided the concentration of this ion in the extracellular fluid is not excessively elevated. Intraventricular block occurs when the concentration is a little more than doubled, and cardiac arrest occurs at levels of from 14 to 16 millimols per liter.

In September 1945, a 12 day old white girl was admitted to the Harriet Lane Home, Baltimore, with the complaint that she had had numerous watery diarrheal stools for two days prior to admission.

The physical examination revealed a dehydrated, emaciated infant who was acutely ill. There was loss of cutaneous turgor, depression of the anterior fontanel and sunken eyes.

During the first three days of hospitalization the infant was given nothing by mouth. During this period she received intravenously and subcutaneously 100 cc. per kilogram of body weight of a solution having approximately the following composition: potassium, 35 millimols; sodium, 122 millimols; chloride, 104 millimols; lactate 53 millimols per liter.

In addition, sufficient 5 per cent dextrose solution was administered intravenously to make the fluid intake up to 200 cc. per kilogram of body weight per day. Toward the end of the third day in the hospital, the stools were normal and the general condition of the patient had improved. The following day milk feeding was resumed.

On the tenth hospital day the infant again began to have large watery stools and to show evidence of dehydration, despite a fluid intake of 175 cc. per kilogram of body weight. The feeding was discontinued and 200 cc. of the potassium chloride–sodium chloride–lactate solution was injected subcutaneously without any preceding administration of a salt solution.

One hour later examination revealed the infant cyanotic and listless. The heart rate was 80 beats per minute and an electrocardiographic tracing showed evidence of severe potassium intoxication with first degree heart block, inversion of the T wave, isoelectric P waves and intraventricular block. A potassium determination made on a blood sample drawn at this time showed the level of potassium in the serum at 12.27 millimols per liter.

The prompt administration of 15 cc. of calcium gluconate intravenously and of 150 cc. of hypertonic dextrose solution produced an immediate response. Within one hour the electrocardiographic tracing revealed that the heart rate had risen from 80 to 110 beats per minute, and two hours after the initial therapy, a third electrocardiogram revealed complete recovery. The infant continued to improve and was discharged in good condition.

The potassium intoxication evident in this 3,000 Gm. (6 pound 9 ounce) infant was manifest one hour after a subcutaneous infusion of 200 cc. of the potassium chloride–sodium chloride–lactate mixture. The amount of potassium (8 millimols) administered, even if it had been absorbed immediately, was enough to raise the extracellular potassium concentration only 5 millimols per liter. Yet at the onset of the intoxication, the level of potassium in the serum was 12.27 millimols per liter. This high level may be explained on the basis that the administration of potassium during the first diarrheal episode resulted in a replacement of any deficit of cellular potassium and allowed it to accumulate in the extracellular fluids. Oliguria was also a contributing cause.

In treating this infant, the calcium ion was supplied to counteract the inhibitory effect of potassium on the heart. The hypertonic solution of dextrose was given not only as a diuretic but also to enhance the deposition of glycogen and potassium in the liver.

This case demonstrates that prompt and specific therapy will relieve severe potassium intoxication.

AUTHORS' ABSTRACT.

ESTABLISHMENT OF A TRANSFUSION CLINIC: TREATMENT OF MEDITERRANEAN ANEMIA IN THE OUTPATIENT DEPARTMENT. PHYLLIS KOTEEN and NATHALIE BROOKS, J. Pediat. **28**:697 (June) 1946.

The successful management of severe familial erythroblastic (Mediterranean, Cooley's) anemia requires frequent blood transfusions. It is only since the introduction of this therapeutic agent that a few children with this illness have survived to and beyond adolescence. The disease in those patients was not comparable in severity to that in the cases to be described. However, irrespective of the apparent severity of the disease, there is always the possibility of spontaneous remission, an outcome which has been observed in a few cases at the New York Hospital. It is essential, therefore, that all efforts be made to keep patients with this illness alive.

Six children with the severe form of familial erythroblastic anemia have been followed at the New York Hospital for several years. They vary in age from 2 to 10 years. They have required frequent hospitalization for transfusions and for illnesses which often accompanied the anemia—these illnesses usually involved the upper or lower respiratory tract, but cardiac complications were not uncommon. The youngest child has been hospitalized seven times and the oldest forty-five times. The total number of patient days in the hospital for the group was 1,774, and the total number of transfusions was 651, consisting of 101,800 cc. of blood. Admissions were becoming more frequent as the patients grew older, and normal continuity of home and school life was impossible.

In March 1944, a transfusion clinic was established to treat these patients on an ambulatory basis. Initially, only 2 children were accepted for the clinic; but subsequently all 6 have been added to the group. Since joining the clinic, the entire group has been well except for minor infections of the respiratory tract.

The children have required no hospitalization and have been regular in school attendance.

The equipment used consists of a transfusion set, sterile gauze, medicine glass, sterile isotonic solution of sodium chloride, tourniquet and adhesive tape. The transfusion set is equipped with a three way stopcock, so that blood can be either pumped in or allowed to flow by gravity. For several months, a suspension of type O red blood cells in isotonic solution of sodium chloride or in 10 per cent corn syrup was used exclusively. This suspension was obtained from the Red Cross blood donor center. Since the end of the war the blood cells have been unobtainable, and whole bank blood is used instead. The authors found the latter more efficacious in maintaining good hemoglobin levels.

Each patient requires 1 pint (473 cc.) of blood approximately every two weeks. After the blood count and cross matching have been carried out, the transfusion is begun. One hour is allowed for the completion of each transfusion. After this, the child remains quiet for one hour, and then, if no severe reaction has occurred, he may go home.

The reactions so far encountered have consisted of fairly frequent fevers, chills and headaches; occasional bouts of asthma, and one severe hemolytic reaction. None of the reactions has been severe enough to warrant hospitalization.

The authors summarize their observations as follows: An outpatient department transfusion clinic has been established and conducted successfully for twenty months. Six patients with severe familial erythroblastic anemia have been treated here and have remained well during this period; a similar clinic could probably be organized to treat any form of chronic anemia requiring repeated transfusions at intervals.

FROM THE AUTHOR'S ABSTRACT.

THE ABSORPTION, DISTRIBUTION AND EXCRETION OF STREPTOMYCIN. E. K. MARSHALL JR., J. Pharmacol. & Exper. Therap. **92**:43, 1948.

This study was made on 1 man and 2 dogs; the determination of streptomycin was performed by clinical methods. The plasma concentration of streptomycin given intramuscularly reached the level of that given by vein in about an hour and then remained somewhat higher than when given by vein. Nearly all the drug was excreted in the urine of the dog but not always in that of the man. The larger part of the dose of streptomycin was excreted in six to eight hours.

PILCHER, Cleveland.

INFLUENCE OF BAL ON THE TOXICITY AND CHEMOTHERAPEUTIC ACTIVITY OF MAPHARSEN. N. ERCOLO and WILLIAM WILSON, J. Pharmacol. & Exper. Therap. **92**:121, 1948.

The experiments were made on albino mice. The essential data are given in the summary as follows: The curative activity of oxophenarsine hydrochloride (mapharsen®) is inhibited by much lower doses of BAL than the trypanocidal activity. The therapeutic activity of the arsenical compound is inhibited by relatively lower doses of BAL than the toxicity, as measured by mortality figures.

In general, the higher the dose of the arsenical drug the more BAL proportionately is required for inhibition. The extremely rapid decrease in the curative action of oxophenarsine hydrochloride, when given in conjunction with BAL, precludes the possibility of this form of combined chemotherapy.

FROM THE AUTHORS' SUMMARY.

THE EFFICACY OF BAL (2, 3-DIMERCAPTOPROPANOL) IN THE TREATMENT OF EXPERIMENTAL LEAD POISONING IN RABBITS. FREDERICK G. GERMUTH JR. and HARRY EAGLE, J. Pharmacol. & Exper. Therap. **92**:397, 1948.

The present authors and others have shown that BAL (British antilewisite) has been effective in the treatment of arsenic poisoning in man and animals and of antimony poisoning in animals. In this work on rabbits poisoned by subcutaneous or intravenous irrigations of lead acetate BAL had no demonstrable protective action and at times actually accelerated the toxic effects of lead acetate in rabbits. It was observed, however, that BAL did cause a striking increase in urinary exretion of lead.

The authors point out that this seeming paradox may be due to the fact that relatively large quantities of lead are needed to kill rabbits and that enough lead is not excreted to save lives or that the combination of lead and BAL may itself be toxic. Despite the present complete failure of BAL to detoxify lead in rabbits, its effect on the urinary excretion of lead was so striking as perhaps to justify its cautious therapeutic trial in human cases.

PILCHER, Cleveland.

A COMPARATIVE STUDY OF THE INTRAVENOUS PIGEON AND THE INTRAVENOUS CAT METHOD IN THE ASSAY OF DIGITALIS. HERBERT A. BRAUN and LEHMAN M. LUSKY, J. Pharmacol. & Exper. Therap. **93**:81 (May-Aug.) 1948.

While the indications for the use of digitalis are much less frequent in children than in adults, the results of this study are of great interest to the pediatrician as they indicate that digitalis preparations now available are of practically equivalent potency. The study was made on pigeons, as it is known that they respond fairly uniformly to digitalis, more so than cats.

The results showed that the estimates of potency for thirty digitalis products obtained by this method varied in no case by more than 13.6 per cent from those obtained by the present U. S. P. method. The average deviation between the two methods was not significantly different from 0. The coefficient of variation of the lethal dose of digitalis for the pigeon in these tests was 10.4 per cent, as contrasted to 12.9 per cent for the cat.

PILCHER, Cleveland.

A PEDIATRICIAN REPORTS ON DUTCH CONCENTRATION CAMPS. S. VAN CREVELD, Arch. franç. de pédiat. **3**:493, 1946.

The author describes his tour of several concentration camps where 20,000 children were confined during the years following 1942 and where starvation, disease and studied neglect brought an untimely death to most of them. Van Creveld finds it impossible to believe that such crass brutality and such utter abandonment of all the dictates of mercy have ever been equalled, among either barbarous or so-called civilized populations. At the camp in Vught, particularly, conditions were so insufferable that "Dante's Inferno would have resembled Paradise." A stern rebuke for those responsible is included.

AMESSE, Denver.

PEDIATRICS IN THE WORKS OF AMBROISE PARÉ. V. J. ANELLO, Arch. argent. de pediat. **27**:66, 1947.

A discussion is given of the knowledge of pediatrics in France during the sixteenth century, with reference to the works of Ambroise Paré.

ROJAS, Boston.

Society Transactions

AMERICAN PEDIATRIC SOCIETY

Jean Valjean Cooke, M.D., President

Fifty-Ninth Annual Meeting, Atlantic City, N. J., May 5 and 6, 1949

Presidential Address. Dr. Jean Valjean Cooke, St. Louis.

Quantitative Method for Measuring Hemophilus Pertussis Antibody. Dr. Hattie E. Alexander, Dr. Catherine MacPherson and Winifred Redman, New York.

The increased use of Hemophilus pertussis antiserum, both human and rabbit, in the treatment of whooping cough, emphasizes the need of better criteria for judging the size of the dose required for the most efficient therapeutic action. Experience with other therapeutic antiserums suggests that the amount of antibody needed for a given patient varies with the size of the patient and the severity of infection. Two essential requirements have been studied: (1) a quantitative method for measuring antibody and (2) an objective method for determining adequacy of dosage.

The antibody in human and rabbit H. pertussis antiserums has been measured in milligrams per cubic centimeter by a quantitative method for determining agglutinin nitrogen. The results demonstrate that the rabbit is a more efficient producer of H. pertussis antibody than is man. Preliminary experiments suggest that this method measures the protective or curative element in therapeutic antiserums. A criterion is offered for judging the adequacy of dosage in a given patient.

DISCUSSION

Dr. William L. Bradford, Rochester, N. Y.: There has been some objection to the use of rabbit serum on the basis of sensitization. This reaction has not occurred to a significant degree in my experience. Aside from the demonstration of the relatively high content of antibody in rabbit serum, I think Dr. Alexander's contribution suggests a useful method with which to measure the antibody content of human serum. In this connection, I should like to ask her whether she has applied her method to the study of children before and after active immunization.

Dr. Benjamin Kramer, Brooklyn: Was Dr. Alexander's human serum one of her own preparation or one of the concentrated or unconcentrated purified serums now available commercially?

Dr. John A. V. Davies, Boston: A day or so after a first determination, I noticed that the antibody titers were equal to, or in some cases higher than, those obtained at first. Does Dr. Alexander have any explanation of this? Does it have any bearing on the route by which the serum should be given; is there, for example, any advantage in having a high titer immediately? Has Dr. Alexander any figures on the titer after a few hours?

Dr. Hattie E. Alexander, New York: In answer to Dr. Bradford's question, we have not measured the antiagglutinin nitrogen in patients who have been immunized. On the other hand, pools of serum from adults and from infants under 6 months of age have been analyzed by this method; in infants under 6 months

of age, we were unable to measure agglutinin nitrogen. In the adult group, the results can be considered only preliminary, but the values for agglutinin nitrogen were almost comparable with those in the human therapeutic antiserums. In other words, apparently, most adults do have a measurable amount of agglutinin nitrogen.

In answer to Dr. Kramer's question, both human serums used were commercial products. The first was the gamma globulin fraction. The second was a lyophilized serum which was reconstituted to one half of its original volume.

In answer to Dr. Davies' question, I believe the increase seen at times in the concentration of antibody in patients' serums is possibly due to the fact that not all the antibody is absorbed from the intramuscular source within the two day period. We have had measurements only at one other early period—at twenty-four hours. The antibody concentration was much less than that at forty-eight hours. That is the reason we chose the forty-eight hour period for the first measurement. I believe that in the seriously ill infants intravenous antibody therapy is indicated. I think we are all aware that gamma globulin produces severe reactions when given intravenously; on the other hand, I understand from Dr. A. C. McGuinness, of Philadelphia, that the lyophilized human serum can be given intravenously quite safely without untoward reactions.

Action of Aureomycin, of Polymyxin B and of Streptomycin on Experimental Murine Pertussis. Dr. William L. Bradford and Elizabeth Day, Rochester, N. Y.

Groups of 3 week old white Swiss mice were given intranasal injections of suspensions of freshly isolated Hemophilus pertussis. The therapeutic action of aureomycin was tested and compared with that of polymyxin B and of streptomycin. The control groups of mice were given injections of 0.85 per cent salt solution. The mortality rates were calculated by the 50 per cent end point method. Surviving mice were autopsied at the end of a ten day period and cultures of the lung made to determine the persistence of the organism.

The results were as follows: Aureomycin in a concentration of 25 to 50 micrograms per cubic centimeter of solid medium inhibited the growth of H. pertussis. Daily doses of 10 and of 100 mg. per kilogram of body weight per day protected mice during the period of treatment against 250 minimum lethal doses of the organism instilled intranasally. The action appeared to be bacteriostatic rather than bactericidal, for deaths frequently occurred within ten days after cessation of therapy.

Polymyxin B in concentrations of 0.5 to 1 microgram per cubic centimeter of solid medium inhibited the growth of H. pertussis. Daily doses of 1 and of 10 mg. per kilogram of body weight protected mice against the experimental disease.

H. pertussis was observed to be sensitive to streptomycin in concentrations of 0.4 to 1.2 micrograms per cubic centimeter of solid medium and protected mice against the experimental disease in therapeutic daily doses of from 50 to 100 mg. per kilogram of body weight.

DISCUSSION

Dr. Hattie E. Alexander, New York: The work of my colleagues and me with the new antibiotic substances and Hemophilus pertussis has been limited to in vitro tests, but some of the results are of interest. Dr. Bradford mentioned the lability of aureomycin in vitro. For that reason, we read the results of our tests for the minimal effective concentration at twenty-four hours; in those circumstances, the concentration required for effective inhibition against an inoculum of 10,000,000 organisms per cubic centimeters is quite low.

We have been interested in comparing the efficacy of aureomycin with that of chloramphenicol (chloromycetin®) against a number of gram-negative bacilli. The latter agent is much more stable and, so far, has no toxic effects, not even the irritating action on the gastrointestinal tract which it is already clear aureomycin has.

We have not been able to demonstrate a significant difference between the concentrations of aureomycin and chloramphenicol necessary for inhibitory action against H. pertussis, if we take our readings for tests with aureomycin after twenty-four hours' incubation. But there is a significant difference when one tests the speed of the bactericidal action of these two agents against a constant number of organisms. Chloramphenicol is clearly, in our experience, more rapidly bactericidal. Within a small population, aureomycin exerts a significant degree of bactericidal action. It appears from in vitro experiments that chloramphenicol should be a more valuable therapeutic agent.

Dr. Horace L. Hodes, Baltimore: My associates and I have tested in the laboratory three of the antibiotic substances mentioned. Polymyxin D proved to be most effective in protecting mice infected intracerebrally with Hemophilus pertussis. It was more effective than aureomycin and streptomycin. In the treatment of the disease in infants, the results with these antibiotic drugs, in our experience, have been inconclusive. Polymyxin D did appear to have some effect on the course of the disease in babies, but all the infants treated showed albuminuria, so that the use of this antibiotic substance was discontinued.

From a clinical standpoint, it seems clear from our experience that antipertussis rabbit serum given promptly is the best therapeutic agent. Thus far, the results with aureomycin chloramphenicol (chloromycetin®) and streptomycin have been inconclusive. Polymyxin D should not be used because of its toxicity.

Dr. William A. Reilly, Little Rock, Ark.: My colleagues and I have worked for a year and a half with streptomycin. We have been favorably impressed. We used it with young infants particularly, and, among 25 or 30 of them, only 2 died. The therapeutic response has been dramatic. In a matter of several days, these children have had a striking reduction in paroxysms of coughing; the cultures have become negative, and the organism was no longer to be found. What is Dr. Bradford's impression of the clinical value of the three agents?

Dr. Samuel Z. Levine, New York: In Poland, which I visited last summer, there was a high incidence of whooping cough. It was being treated routinely on an ambulatory basis with streptomycin. In the University of Posnan, for example, at the time I was there, 120 infants under 1 year of age were being treated with streptomycin in the outpatient department with what the workers reported as remarkably successful results. There were no deaths and no complications. From the clinical point of view, apparently, the results these men have obtained with streptomycin, which incidentally is freely available in Poland, differ from those Dr. Hodes reported, especially in regard to complications in infants under 1 year of age. In any case, the method of therapy in Poland was effective with streptomycin as the only agent used.

Dr. Jerome L. Kohn, New York: In a study I made with Dr. A. Fisher and Dr. S. Kaplan, polymyxin B was given to 64 children with whooping cough, usually during the second or third week of illness. Toxic effects were noted in all patients given intramuscular injections. Toxicity was manifested by fever, albumin and cellular elements in the urine and lethargy, irritability and anorexia. In all instances, the toxic symptoms were transient and subsided with the discontinuance of treatment. With the dosage used, the clinical results were unfavorable. Because of the toxicity of the drug the study was discontinued.

In another study we treated more than 200 children with streptomycin by (1) intranasal drops, (2) intramuscular injections and (3) aerosol mist. The nasal drops had no therapeutic effect. We had the impression that streptomycin when administered by aerosol mist or intramuscular injection favorably influenced the course of the whooping cough. There was no evidence that the administration of polymyxin B or streptomycin in the dosage used had any effect on the presence of Hemophilus pertussis organisms.

DR. WILLIAM L. BRADFORD, Rochester, N. Y.: Concerning the relative merits of the various therapeutic agents, I regret that I am a poor informant. The extreme variability of the clinical disease and the lack of sufficient clinical material in our clinic have contributed to this situation. We observed that streptomycin when used as an aerosol has a favorable effect on the clearance of the organism from the respiratory tract. In certain instances, when micronized streptomycin was used, the organism rapidly became resistant. In our clinic, we have come to rely on the combination of sulfadiazine and pertussis immune serum (rabbit) for the treatment of seriously ill infants. In fact, it is sometimes difficult to restrain the house officers from immediately instituting this form of therapy. Dr. Levine's remarks concerning his observations in Poland are interesting. Surely, if streptomycin is to be used, it should be given early in adequate dosage and its administration discontinued before unfavorable effects on the host occur.

Present Status of Serologic Tests in the Diagnosis of Acute Rheumatic Fever. DR. T. N. HARRIS and DR. SUSANNA HARRIS, Philadelphia.

We do not at present know the specific etiologic agent of rheumatic fever, such as would properly be used as antigen in a serologic diagnostic test for this disease. In these circumstances, the association of rheumatic fever with streptococcic infections has been used in attempts to arrive at such a test. Thus, the titer of neutralizing antibodies to streptococcus hemolysin has been measured in serums of patients with acute rheumatic fever in an attempt to determine the clinical status of these patients. Unfortunately, the range of antistreptolysin titers observed in this infection is not different from that observed following acute streptococcic infection. Other streptococcus antigens have shown the same limitation. In the case of tests with neutralizing antibodies to streptococcus hyaluronidase, however, more than a third of the patients with acute rheumatic fever thus far studied have shown titers above the range we observed following streptococcic infection. The ranges of streptococcus antihyaluronidase and antihemolysin titers in persons with acute and quiescent rheumatic fever, those convalescing from streptococcic infection and the normal population indicate other advantages of the use of the antihyaluronidase test in the diagnosis of acute rheumatic fever and in the detection of recrudescences of activity in this disease.

DISCUSSION

DR. IRVINE MCQUARRIE, Minneapolis: To add more confusion to this general problem of the antihyaluronidase test and the erythrocyte sedimentation rate, a new observations has been made by Dr. Robert Good and Dr. Vincent Kelly, of Minneapolis, who reported on their studies at the meeting of the Federation of American Societies for Experimental Biology, in Detroit, April 18 to 22, 1949.

They observed that the mucoproteins, which constitute a small fraction of the total serum proteins, rise to several hundred per cent above normal in active rheumatic fever, and one can determine that fraction by chemical means, fortunately. It tends to parallel, in general, the antihyaluronidase titer Dr. Harris

spoke of, and the sedimentation rate as well. But, in some cases of acute active rheumatic fever the increase was more striking than the change in the serum antihyaluronidase titer. The fraction was normal or low in these cases between active attacks. It was not increased in uncomplicated chorea. The fraction was higher, as Dr. Harris showed for antihyaluronidase, in cases of active rheumatic infection than in cases of other streptococcic infections, such as uncomplicated pharyngitis. The rheumatic infection, then, is somehow associated with the rise in this fraction. The rise is not specific for rheumatic fever but may be a good index of disease activity. Subsequent work on the subject, which will be reported on in the near future by Glick and these two men, indicates that the fraction is an entity different from the hyaluronidase inhibitor. At least, the results are not always correlated as one might expect if it were the same as the inhibitor substance. Just how practical determination of the mucoprotein fraction will be as a test of activity, I do not know. One can determine the fraction in the ordinary clinical laboratory, which makes the method available as an additional test for rheumatic activitiy.

DR. SAMUEL Z. LEVINE, New York: Similar studies with bovine testicular hyaluronidase, which were recently completed in the cardiac clinic at New York Hospital, showed completely antithetical results, which might be expected in view of the specificity of the streptococcus hyaluronidase. There was no elevation in the inhibitor substance in persons with rheumatic fever, in those with active rheumatic fever, in those in the quiescent state or in those without rheumatic fever. Furthermore, no change in titer occurred during the progress of rheumatic fever from the acute episode through convalescence.

The explanation, apparently, is obvious from Dr. Harris' report. I wonder whether additional control studies, Dr. Harris, were done with pneumococcus hyaluronidase or with the hyaluronidases derived from other bacteria besides streptococcus and whether any tests were done against human hyaluronidase per se.

DR. T. N. HARRIS, Philadelphia: Extensive serologic control studies were made, involving pneumococcic and bovine testicular hyaluronidase. They are described in the first lengthy report of this work (*Am. J. M. Sc.* **217**:174-186 [Feb.] 1949). These serums, most of which had been stored for some time in a frozen state, had lost this labile bovine antihyaluronidase; in the case of pneumococcus hyaluronidase, there were a few slightly elevated antibody levels but none in correlation with the higher levels of streptococcus hyaluronidase.

We have not used the human hyaluronidase. The bovine type is much easier to obtain, and I think that the results would be similar, that is, a nonspecific inhibition with the action of hyaluronidase rather than a neutralization of the enzyme on serologic grounds.

Chorioretinopathy Associated with Other Evidence of Cerebral Damage in Childhood: A Syndrome of Unknown Origin Separable from Congenital Toxoplasmosis. DR. ALBERT B. SABIN and DR. HARRY A. FELDMAN (by invitation), Cincinnati.

Ever since chorioretinitis and cerebral calcification were recognized as important manifestations of congenital toxoplasmosis, this disease came to be considered in differential diagnosis whenever one or the other of these signs was observed to be associated with other evidence of cerebral damage. The serologic methods for the diagnosis of toxoplasmosis available up until about a year ago were crude, qualitative rather than quantitative and incapable of differentiating between the antibody response due to toxoplasmic infection of relatively recent date and that

resulting from exposure to Toxoplasma (or some other agent containing a related antigen) in the more distant past. The recent development of the in vitro dye test for the quantitative determination of toxoplasmic antibody and of an improved complement fixation test has greatly enhanced the reliability of the serologic diagnosis of congenital toxoplasmosis. These newer methods were applied to the study of serums from children exhibiting various cerebral and ocular changes believed to be of congenital origin and to the serums of their mothers residing in various parts of the United States and Europe. Thus, in a group of 24 children up to 7 years of age in whom definite serologic evidence of congenital toxoplasmosis was obtained, cerebral calcification was associated with the chorioretinitis in all but 2, and these 2 we have not yet had an opportunity to examine the roentgenograms. On the other hand, in another group of 18 children, ranging in age from a few months to 6 years, who exhibited ocular changes generally described as chorioretinitis (but which might well represent degenerative or atrophic lesions of the retina) associated with other signs of cerebral damage (hydrocephalus, microcephaly, convulsions, cerebral atrophy and mental retardation) but without roentgenologic evidence of cerebral calcification, there was no serologic evidence of congenital toxoplasmosis. Thus, it appears that when chorioretinopathy is present together with other signs of cerebral damage in early childhood the chances are 90 per cent or better that the disease is not due to congenital toxoplasmosis if careful examination of the roentgenogram of the head reveals no cerebral calcification. The same probability may not apply to chorioretinitis first discovered in later childhood, but further studies by the newer methods are needed. In the absence of both cerebral calcification and chorioretinitis, the chances that cerebral damage in childhood is due to congenital toxoplasmosis are practically nil on the basis of the serologic studies carried out by the newer, as well as the older, methods.

DISCUSSION

DR. SIDNEY FARBER, Boston: It would be surprising, indeed, if causation of any group of pathologic changes as striking as these in the brain, eyes and viscera was limited to any one agent; Dr. Sabin has brought out clearly that other conditions may simulate the clinical picture produced by toxoplasmosis.

I should like to make particular reference to a paper which two of my colleagues, Dr. Edward B. D. Neuhauser and Dr. Arthur Tucker (*Am. J. Roentgenol.* **59**: 805, 1948), published about a year ago concerning the occurrence of ocular changes and cerebral calcification in infants 1 to 2 months of age, with symptoms dating from birth caused, as they said, by infection with Cryptococcus neoformans. Since our laboratory was responsible for that diagnosis, I should like to record the fact that a review of this material sent to Dr. Sabin because of his work in the field raised the question in his mind whether this agent had anything to do with these lesions at all. Dr. Sabin's opinion was that they were merely further examples of toxoplasmosis.

In the first case, animal inoculation was carried out by Dr. John Davies and his group, and no evidence of toxoplasmosis was found. In the second and third cases, the bacteriologic and animal studies carried out by my colleague, George Foley, showed that C. neoformans was present. His studies have been in progress for almost two years on the biologic aspects of these organisms.

Because Dr. Sabin could not accept our diagnosis, because he observed in these cases organisms which he regarded as typical of Toxoplasma and because he found further serologic evidence in specimens sent to him by our group, I wish to state here, for the benefit of those of you who have read the paper by Dr. Neuhauser and Dr. Tucker, that the question of the cause of these lesions must be kept open.

My own opinion, however, is that the Cryptococcus organisms appear to be present in the tissues in a state sufficiently clear to satisfy criteria which I would demand and that organisms which appear to be Toxoplasma are also present. The question, therefore, whether the C. neoformans is capable of causing cerebral calcification in the neonatal period with the clinical picture apparently identical to that produced by toxoplasmosis should be left open until further studies by our group bring evidence sufficient to please Dr. Sabin and others who are working with these organisms.

DR. BENJAMIN KRAMER, Brooklyn: Did any of these children have vascular nevi? The syndrome of Parke-Weber is well known. In it, vascular nevi are associated with cerebral calcification and mental retardation.

DR. ALBERT B. SABIN, Cincinnati: There were no vascular nevi in the children who presented these peculiar vascular malformations in the brain or in any of the other patients with chorioretinopathy. In calling this a syndrome of unknown origin, I am fully conscious of the fact that further studies will unquestionably reveal a multiple etiologic basis.

Does Modified Measles Result in Lasting Immunity? DR. SAMUEL KARELITZ, New York.

An attempt was made to answer this question by querying almost 500 pediatricians. The study is continuing, but available data seem sufficient to warrant the expression of an opinion. Questionnaires were sent to 250 pediatricians throughout the United States and Canada, who were selected from the directory of the American Academy of Pediatrics, and to a few in Europe. More are being sent now. This group of physicians was selected because they were known to be interested in measles prophylaxis, to have large pediatric practices or to be teachers of pediatrics. In addition, approximately 250 practicing pediatricians of New York, Westchester, Long Island, New Jersey and Connecticut were questioned directly.

Ninety questionnaires were answered and others are still arriving, many of them by persons with extensive experience in measles prophylaxis. Of this total, only 13 indicated that they had observed or knew of the occurrence of measles in persons who previously had had modified measles. A total of 26 cases were reported, of which several (8) were doubtfully significant.

Dr. C. F. McKhann observed only 2 cases among approximately 4,000 persons inoculated. Four noted more than 1 person per family to have had measles after modified measles. In view of the small total number of cases reported, this familial incidence permits of interesting speculation. Officials of three pharmaceutical firms which distributed placental globulin, and later gamma globulin preparations, indicated that they were unaware of the occurrence of measles following modified measles. The combined amount distributed by the three firms was great, that of one firm alone being 2,500 liters of the older globulin preparations and 400 liters of the alcohol-fractionated material to date, or approximately 1,000,000 prophylactic doses.

I have been interested and actively engaged in the study of measles prophylaxis since 1925 and have observed a large number of cases of modified measles. On only one occasion and possibly in another instance have I seen definite measles after an undoubted case of modified measles.

Measles prophylaxis has been practiced commonly for about twenty years and extensively since the introduction of human globulin preparations, or for about fifteen years. Since measles is a common disease recurring in epidemic form every two to three years and since 95 per cent of the cosmopolitan populations have

had measles prior to the age of 21 years, it is likely that a large number of persons who had modified measles have received challenge infections. The small number of cases of measles occurring after modified measles here reported suggests strongly that modified measles usually, but not always, confers lasting immunity. Further data are being accumulated.

DISCUSSION

DR. HORACE HODES, Baltimore: Could Dr. Karelitz give us information regarding the incidence of encephalomyelitis. One gets the impression that children with encephalomyelitis have had a severe attack of measles.

DR. CHARLES A. JANEWAY, Boston: It seems to me that the conclusions of Dr. Karelitz are in line with the experience my colleagues and I have had. A few persons in the practice of medicine will often state that they have seen many attacks of measles after modified measles, but it has been my experience that, generally, when one tries to trace these down, they prove to be but a small number of only probable cases.

We have been much interested in this problem because it seemed to us at the time of the introduction of gamma globulin that two important questions had to be answered if measles modification were to become a routine pediatric procedure. These two questions are, first, the one Dr. Karelitz has posed, does one obtain a lasting immunity to modified measles, and, second, does modified measles result in a much lower incidence of encephalitis? Since mortality from measles depends on the occurrence of septic and central nervous system complications, and since the permanent damage from the disease, in terms of bronchiectasis or mental retardation, is the result of these types of complications, it seems important to determine the answer to both these questions.

The only evidence which I can give concerning complications is that, in a series of patients in whom gamma globulin had been used, among the small number of patients to whom gamma globulin failed to give adequate protection so that serious disease ensued, there were 3 with major complications, 2 of them with the septic type and 1 with a severe bout of encephalitis; while in the group whose measles was modified, which was ten times as large, no instances of encephalitis were observed.

It has been our plan, when sufficient time has elapsed, to follow up all patients on whom we have reports—the whole group, not only those who have had modified measles but those in whom measles has been prevented completely—in order to try to determine the answer to Dr. Karelitz's question.

It is quite conceivable that a number of persons who have apparently not had measles at all as a result of protective doses of gamma globulin may be found to have had sufficient attacks by the virus so that they, too, have developed an immunity. Such immunity, although probably not permanent in many, may well increase the percentage of insusceptible persons in this group.

I hope this work will go on. There are many important questions about gamma globulin that are unanswered and which should be answered for the benefit of the practicing pediatricians of the country. We will welcome cooperation in the coming years from any of you interested in this problem and will be glad to supply you with material, if you are willing to report to us so that we can pool our experiences.

DR. SAMUEL KARELITZ, New York: I have had one fascinating experience in the treatment of measles. The child was in the early stage of the disease. He had been exposed in his home to his brother. He had definite Koplik spots. Because he was a deaf-mute we tried to make the disease milder. Therefore, he

was given 30 cc. of convalescent serum intravenously. On the next day he showed a sparse, spotty rash. His temperature never rose over 101 F. thereafter, and his cough disappeared promptly, but five days later he could not be aroused. He slept around the clock. A lumbar puncture yielded spinal fluid with a slightly elevated protein content and with 260 cells, all lymphocytes. As far as I can tell he had a complete recovery. This is the only instance of encephalitis in a case of modified measles of which I know. This child was not treated prophylactically but therapeutically after the disease had started.

I should like to answer Dr. Janeway's question about the possibility of a person's remaining immune if, after exposure to measles, he was given enough gamma globulin to escape a clinical attack. In the past, when convalescent serum was used, that was not possible, because on repeated exposure to measles one could estimate that the passive immunity would last no longer than three to four weeks. Once the question arose whether the passive immunity might have lasted a year, because the child had a mild attack of measles a year after receving measles prophylaxis for another exposure to the disease. I doubt that the passive immunity lasted that long. It is more likely that this child's measles was mild.

I might comment on another question asked earlier. Can one protect children with gamma globulin from blood obtained from nonimmune persons? The answer is no. That was not true of serum obtained from persons who never had measles; I know that I had failures with placental extract and then discovered that the mother from whom that placenta was obtained did not have measles.

Studies of Heart Volume in Infants. Dr. Arvid J. Wallgren, Stockholm, Sweden.

During the last five years roentgenologic determinations of heart volume according to the technic and calculations suggested by Jonsell have been carried out by Dr. John Lind, of the Department of Pediatrics of the Royal Caroline Medical Institute, at Norrtull's Hospital, Stockholm, Sweden. In all, roughly 300 infants were examined. The infant was placed on its back with the arms stretched above its head. Synchronous frontal and lateral exposures at a focal distance of 100 cm. and with an exposure time of 0.02 second were made. Electrocardiographic and respiratory movements were simultaneously recorded. The exposure was made in maximal diastole, just before the R wave. The long diameter of the heart shadow was measured from the base of the large vessels on right side to the apex; the broad diameter was the shortest transverse line from the angle of the heart and liver to the left margin of the heart; the depth was measured from the anterior outline of the esophagus moderately filled with contrast medium to the anterior outline of the heart. These three figures were multiplied with a constant and gave the heart volume in cubic centimeters.

In 10 infants, the heart volume was roentgenologically determined after death and compared with the real heart volume of the removed, paraffin-filled organ. These two determinations showed satisfactory agreement when the errors inherent in the method were taken into consideration. The difference between double clinical determinations without consideration of the phase of the cardiac cycle and the respiration was 5 per cent. The average variation in the volume of the heart in systolic and diastolic phases of the cardiac cycle was 5.7 per cent, and in maximal inspiration and expiration, 5.2 per cent. As stated previously, the exposures were made during maximal diastole.

The heart volume per square meter of body surface increased gradually with increasing age of the infant, while the volume per kilogram of body weight remained constant, with a slight decrease at 6 to 12 months of age. The heart volume in

premature infants was 200 cc. ±4.3; in infants below 3 months of age, 230 cc. ±2.3; in infants 3 to 6 months of age, 260 cc. ±4.4; in infants 6 to 12 months of age, 260 cc. ±4.9; in infants 1 to 2 years of age, 264 cc. ±7. In children 12 to 14 years of age, the heart volume was 315 cc., and in persons 20 to 30 years of age, 372 cc.

Physiologic and Chemical Response of Premature Infants to Oxygen-Enriched Atmosphere. Dr. Bruce D. Graham, Dr. Helen S. Reardon, Dr. James L. Wilson, Dr. M. U. Tsao and Mary L. Baumann, Ann Arbor, Mich.

Irregular respiration of premature infants has been attributed to immaturity of the respiratory center or respiratory muscles, differences in nature of hemoglobin and unsaturation of blood with oxygen.

Qualitative changes in respiration of premature infants due to the administration of oxygen have previously been shown (Wilson and others: Respiration of Premature Infants, Am. J. Dis. Child. **63**:1080 [June] 1942). This is a report of a further study correlating 29 plethysmographic respiratory records with chemical changes of premature infants while in atmosphere and in oxygen-enriched air. Forty-four samples of arterial blood were analyzed for oxygen content, oxygen capacity, p_H, carbon dioxide content and hematocrit and hemoglobin concentration. Seventy-five per cent of the infants studied breathed with some degree of periodicity or irregularity while in atmosphere; the other 25 per cent breathed regularly. Eighty-eight per cent of the group breathed regularly in 80 to 90 per cent oxygen. The average arterial oxygen saturation in atmosphere was 93 per cent, rising to 100 per cent in 70 to 79 per cent oxygen and to 102 per cent in 80 to 89 per cent oxygen (? 2 per cent or more carried by the plasma). With the administration of oxygen-enriched air, higher levels of arterial oxygen saturation were obtained in the infants with higher hemoglobin and hematocrit concentrations. Hematocrit and hemoglobin levels were both higher in infants of the younger age groups.

Analysis of the respiratory records revealed that premature infants seemed to have an under pulmonary ventilation in atmosphere as evidenced by their response to the administration of oxygen. Minute volume was increased by 30 to 35 per cent when 30 per cent or more oxygen was being breathed. The respiratory rate was increased by 30 per cent in 30 to 40 per cent oxygen but fell to the original level when higher oxygen concentrations were administered. Tidal volume gradually increased by 30 per cent in 70 to 80 per cent oxygen. Therefore, the majority of the infants breathed irregularly in air despite apparent adequate oxygenation as determined by arterial oxygen saturation but, nevertheless, responded to addition of oxygen by breathing regularly with increased pulmonary ventilation. Thus, optimum function of the respiratory center, as manifested by regular breathing, was not obtained until oxygen-enriched atmosphere forced the hemoglobin saturation to near 100 per cent. Plasma oxygen was presumably greatly increased, although this was not determined.

The exact mechanism of the periodic type of breathing of these premature infants has not been ascertained or the mechanism whereby oxygen stimulates regular respiration. Neither has it been generally agreed whether a greater or less than normal respiratory stimulus exists in these infants. From our data it appears that these infants have an oxygen lack and that the lack results from a defect in oxygen exchange from blood to tissues rather than from hemoglobin unsaturation.

When carbon dioxide tension was calculated in these infants breathing in air, an average level of 38 mm. of mercury was obtained in spite of actual acidosis

existing. This level is essentially normal or slightly low as compared with the level for adult controls of 39 mm. of mercury and indicates no "fault" in respiratory control from this factor. It remains to be proved what metabolic changes are effected by the administration of oxygen. Does it change a partially anaerobic metabolism to one which is wholly aerobic? Does the increased pulmonary ventilation result from an increased production of carbon dioxide? In our studies we have not yet obtained data regarding a change of carbon dioxide tension or production of organic acids during the administration of oxygen.

Acid-Base Equilibrium and Oxygen, Hemoglobin and Hematocrit Levels in Premature Infants. Dr. Helen S. Reardon, Dr. Bruce D. Graham, Dr. James L. Wilson, M. L. Baumann, Dr. M. U. Tsao and M. Murayama, Ann Arbor, Mich.

Because of suggestive evidence that a partial anaerobic metabolism may exist in premature infants, studies of acid-base equilibrium with determination of hemoglobin and oxygen levels were undertaken as necessarily fundamental. The acid-base studies presented differ from all previous work in the method of collecting specimens, the type of blood analyzed and the values obtained.

Seventy-three premature infants, aged 1 to 65 days and weighing 2½ to 5 pounds (1,134 to 2,268 Gm.) were studied. The majority were considered to be healthy, insofar as it is possible to classify premature babies, and a few were listed as sick, but no babies with severe diarrhea or dehydration were included in the studies. There was no statistical difference in the results between the babies who were classified as well and those listed as sick, so that data on all babies were included in the computation of the final averages.

The blood from the temporal artery was analyzed for p_H, plasma carbon dioxide content, chloride, total protein, total base, hematocrit reading and hemoglobin concentration. Alveolar carbon dioxide tension (pCO_2) and R were calculated. R represented the acid constituents of blood not analyzed in this study and included sulfates, organic acids and phosphates (in those patients in whom phosphates were not analyzed). R was calculated by subtracting the sum of the acid fractions from the total base of the blood. In 13 of the 73 infants, plasma phosphate was determined. In 45 of the 50 well infants, determinations of arterial oxygen content and capacity with acid-base studies were made. Thirty-one of the 45 patients had venous blood analyzed for oxygen content, capacity and p_H. The average results for arterial blood were compared with those from similar determinations made on blood from the femoral artery of 16 adolescent boys used as controls.

Results.—The study revealed that the majority of premature infants had a slight uncompensated metabolic acidosis, with an abnormal partition of all the acid-base fractions as compared with older infants and adults (table 1). In the group in which phosphate levels were analyzed, the value of 4.0 was also subtracted from the total base, which left an R value of 11.0. The p_H, carbon dioxide content and protein were significantly reduced in premature infants. The total base, chloride, phosphate and R were elevated. The averages for alveolar carbon dioxide tension were essentially the same. There was no statistical correlation of p_H and carbon dioxide content to weight at birth, length at birth or age or weight when the samples were taken.

Oxygen studies revealed that the percentage saturation of arterial blood in the majority of premature infants within the first month of life was within the range considered normal for adults. The average arterial oxygen saturation of

45 well premature infants, aged 1 to 49 days, was 92 per cent. The average of the adult controls was 94 per cent. The hematocrit and hemoglobin levels and percentage saturation of blood with oxygen were all decreased as premature infants become older (table 2).

The average difference between arterial and venous oxygen saturation in premature infants seems much lower than others have reported or than we observed in adults. This is particularly true in well young premature infants who had no blood transfusions. The average venous oxygen saturation of 34 patients was 74 per cent, with an average arteriovenous difference of only 18 per cent. Further work must be done on older premature infants who have not had blood transfusions. Thus, three possible explanations are suggested: (1) The hemoglobin does not give up oxygen readily to the tissues, (2) the volume flow of the blood is increased or (3) the tissues do not utilize oxygen readily.

TABLE 1.—*Results of Determinations on Samples of Blood*

	p_H	CO_2 Content, mEq./L.	pCO_2, mm. Hg.	Cl, mEq./L.	Protein, mEq./L.	PO_4, mEq./L.	Total Base, mEq./L.	R, mEq./L.
Premature infants (75)*	7.31	20.1	38	111	12.7	4.1(13)	130	15.0(60) 11.0(13)
Controls (16)	7.43	22.9	36	102	17.0	2.0(13)	134	11.0 9.0

* Numbers in parentheses indicate number of patients.

TABLE 2.—*Comparison of Oxygen Saturation and Hemoglobin Concentration with Age in Premature Infants*

Age, days	1 to 7	8 to 14	15 to 21	22 to 35	36 to 49
Number of patients	19	5	12	7	3
Percentage saturation*	94	93	93	90	79
Hemoglobin concentration, Gm./100 cc.	16.2	16.2	14.8	11.4	9.8

* These figures imply that with increased age and decreased hemoglobin concentration these infants have greater unsaturation of blood with oxygen. Since this is not statistically significant (at 1 per cent level), further investigation is in progress.

We suggest that a relative tissue anoxia exists, possibly owing to the fact that the reaction of hemoglobin of premature infants in respect to oxygen exchange is similar to the reaction of hemoglobin of the fetus in utero. The chronic acidosis of well premature infants is not entirely explained by the present knowledge of renal function. It is well known that anoxia is one cause of acidosis. The evidence presented here suggests that the acidosis of premature infants is caused by tissue anoxia. By presumption, the acidosis is the result of an increase in organic acids and a lower production of carbon dioxide. Further studies are planned to clarify these points.

DISCUSSION

DR. CLEMENT A. SMITH, Boston: I think this work is as important as it is difficult to understand readily. The difficulty arises from the fact that these workers are describing a type of physiology demanding an approach different from that with which we are familiar in older infants, children or adults. One extremely interesting feature of Dr. Reardon's data is that long after premature birth, when the baby should be functioning like a full term infant, these odd physiologic

attributes persist. Whether the peculiarity, which seems to have been strongly suggested, of the difficulty of the tissues in taking oxygen from the blood or the difficulty of the blood in releasing oxygen to the tissues is related to fetal hemoglobin cannot be determined until we have as much knowledge of fetal hemoglobin as we have of adult hemoglobin.

I assume that by *R* Dr. Reardon means the data given in the righthand corner of Dr. Gamble's diagrams. I take it that the increase in this fraction means an increase not only in the so-called strong acids but in the organic acids. The latter substances do not seem to have been as increased in this study as in others, notably that of Dr. Branning (*J. Clin. Investigation* **21**:101, 1942). Are the high chloride levels shown for these babies related to their diet, or do the increases have to do, again, with a peculiarity of the physiologic makeup of the premature infant? The chlorides in Dr. Reardon's patients were considerably above the levels expected in the normal blood of older children. Did not Dr. Reardon find extraordinary wide ranges in the values for these infants, because it has seemed to me perhaps significant, though I do not know how to explain it, that the range of findings for a group of premature babies suggests their ability to tolerate a much wider range of physiologic wandering than full term babies or adults can.

DR. ALLAN M. BUTLER, Boston: I should like to ask Dr. Wilson what the role of the increase in the dissolved oxygen might be in the beneficial therapeutic effect. I ask the question because Dr. Hugh Montgomery, of Philadelphia, has shown an extraordinary increase of oxygen pressure in tissue as the oxygen in the inspired air is increased when there is no increase in the oxygen content of the arterial blood.

The cardiologists have noted for some time an improvement in the clinical condition of patients given oxygen that cannot be correlated with the increase in the oxygen content of the arterial blood.

DR. SAMUEL RAPOPORT, Cincinnati: I am sure that, as Dr. Smith has suggested, the authors themselves have thought of fetal hemoglobin as a possible explanation of the data. It is quite true that little is known about fetal hemoglobin, except that it accounts for a large proportion of the total hemoglobin of normal newborn infants, that the amount decreases with time but that traces may still be present for some months.

Such a time process would explain the drop in the saturation that the authors have observed. Fetal hemoglobin also differs from the adult type in having a much greater affinity for oxygen, that is, the percentage of saturation is higher for any given oxygen tension. That being so, one could explain the small arteriovenous difference that the authors observed. For a given oxygen tension there would be less oxygen delivered to the tissues. I wonder whether the authors have considered the determination of, or determined, the curves for oxygen dissociation on blood drawn from these patients to test this hypothesis. With these data they could tell us whether fetal hemoglobin is a factor.

I was interested in *R*, the undetermined anions, which has been a great mystery. I recall a debate which raged between the New York group—Dr. Atchley and others (*J. Biol. Chem.* **73**:1, 1927; **75**:697, 1927, also Greene and others, *Biochem. J.* **26**:1377, 1932)—and the Peters group (*J. Clin. Investigation* **6**:517, 1928) on this subject. Dr. Peters and his associates were of the opinion that there was a great increase in organic acids in various conditions, for instance, chronic nephritis. It was shown, at least to my satisfaction, that if both phosphate and sulfate levels were determined the increased *R* was satisfactorily explained.

With reference to the first paper, I think that it would have been more informative if the authors had presented the percentages of saturation of hemoglobin after first substracting the figures for physically dissolved oxygen.

In line with Dr. Butler's statement, other workers have suggested, and accumulated evidence, that, possibly, the cerebral metabolism is dependent on the oxygen tension rather than on the oxygen content of the blood. This would explain the improved consciousness of patients when they are placed in an atmosphere rich in oxygen. Apparently, the oxygen tension at the arterial end of capillaries may determine the nutrition of the brain; perhaps that explains the greatly improved performance in respiration of premature infants.

I was puzzled by the increase of respiration that the authors observed in infants placed in an atmosphere enriched in oxygen. That, I am sure, is an unexpected finding. Would it be possible to consider a stimulant effect of increased oxygen, resulting in increased activity of the infants? One way to check this possibility is to measure the total heat production. If that increased with increased respiration, the effect would lose some of its mystery.

DR. N. K. ORDWAY, New Orleans: In line with what Dr. Rapoport suggested, I wonder whether the apparent beneficial effects of the administration of oxygen in high concentration to these infants may have been related, perhaps, to a possible change in their content of carbon dioxide, and thus in p_H.

It was shown by Gibbs, Gibbs, Lennox and Nims (*J. Aviation Med.* **14**:250, 1943), and abundantly proved in studies of aviation physiology during the war, that, at least in part, the deleterious effects of oxygen in low concentrations were related to the change produced in carbon dioxide content, and that oxygen in an even lower concentration could be tolerated if it was administered with some carbon dioxide.

I wonder whether an analogy in reverse may be found here. It is known that in adult human beings—and my associates and I have observed the same phenomenon in dogs—the administration of oxygen in high concentration produces an immediate increase in carbon dioxide tension with a decrease in p_H, i. e., a respiratory type of acidosis. Are the changes in respiration in these children related to acid-base changes rather than to the changes in oxygen concentration of the blood per se?

DR. BRUCE D. GRAHAM, Ann Arbor, Mich.: In regard to the stimulatory effect of oxygen, it has recently been shown, I understand, that by giving animals high concentrations of oxygen, one can obtain as much as a 12 per cent increase in alveolar ventilation. As shown in our studies, we obtained an average increase of 35 per cent, which was considerably more than the percentage which to date is attributed to the direct beneficial effect of oxygen. As to the beneficial effects of oxygen as related to change in p_H and carbon dioxide content, we determined the carbon dioxide content of the blood of a small group of these infants when they were receiving excess oxygen. We observed a drop in carbon dioxide content of 1 to 1½ milliequivalent per liter in some of the infants. Unfortunately, we were limited by the present methods in not being able to determine p_H in the presence of additional oxygen. Therefore, we were not able to record the carbon dioxide tension of the blood of these infants when they were receiving high concentrations of oxygen.

DR. HELEN S. REARDON, Ann Arbor, Mich.: In reply to Dr. Smith's first question, R represents the sulfate, organic acids and inorganic phosphate in those premature infants in whom phosphate was not analyzed. Three points in our data bear on the question whether the chloride composition of the infant's feeding is the cause of acidosis in premature infants. First, among 12 infants in whom

the plasma chloride was found to be normal, there were 9 who had an acidosis. Second, in 7 infants who had a normal hydrogen ion concentration and total carbon dioxide content, the plasma chlorides were elevated to an average value of 110 milliequivalents per liter and the total base to an average of 109 milliequivalents per liter. The third point is that we took samples on 7 newborn premature infants before any feedings were instituted, and they were found to have the same chemical values for p_H, total carbon dioxide content, chloride and so forth as did babies who had been fed, that is, older infants in the study. In other words, the chloride composition of the infant feeding may be a contributory factor to acidosis, but we do not believe it is the primary cause.

In reference to Dr. Smith's third question about the range of chemical findings in premature infants, I think the last two columns on slide 6 are informative. The adult range for any one of these figures is fairly narrow, for example, the range for carbon dioxide content is 23.1 to 26.4 milliequivalents per liter; whereas the premature infants had a tremendous range which was also shown on the tricoordinate graph [slide 6].

We have not made oxygen dissociation curves, although work on oxygen tension is in progress at present and we think the results will help us with the problem. Dr. Rapoport, I believe, commented on the difference of R of 4 milliequivalents per liter which we found between the adults and the infants. We accounted for 2 milliequivalents per liter by the elevated phosphate determination, but Dr. Rapoport suggested the other 2 milliequivalents per liter may be due to elevated sulfate values. That means that the sulfates would have to be elevated to a total value of at least 3 milliequivalents per liter because we have already accounted for the sulfate within the R of both the premature infant and the adult. Dr. Rapoport's assumption may be true, but I think the few determinations that have been done by other workers do not suggest that sulfates are elevated in premature infants.

Dr. James L. Wilson, Ann Arbor, Mich.: Of course, these data to us raise more questions than they answer. We have spent much time in simply collecting basic data on normal infants. The interpretation of their meaning has to be followed with an immense amount of work. Possibly, we can do some of it, but most of it, I am afraid, will be beyond our capacity.

To answer the direct question of Dr. Butler to me about the effect of the dissolved oxygen, it seems to us that this finding of essentially normal hemoglobin saturation, which was a surprise to me, forces us to believe that physically dissolved oxygen plays a large part in the effects which we have described here. I am sure that we will find out much more once we can learn to determine the plasma oxygen levels directly, instead of having to calculate them.

I might add one criticism. The observation of increased ventilation which seems apparent from the effect of oxygen administration rests on our calculation from measurements of these tracings. I know of no direct measure of alveolar ventilation, although we would like to have one. We are surmising that such a thing takes place because of an increased rate. We have not brought into consideration the really important physiologic effect of different shapes of the curve for respiration, and as our own staff in Ann Arbor pointed out to us—and as Dr. Graham mentioned—although we may have mathematical evidence from our data that such an increased ventilation occurs, we do not yet know its physiologic significance. Actually, we have not proved that there was an increased alveolar ventilation from the effect of oxygen. It was mentioned, I believe, that possible increase of ventilation, if it is true that it occurred, might well be due to an increased production of carbon dioxide, but we have been unable to prove that with the data presently available.

Obstacles to Measurement of Electrolyte Balances. Dr. James L. Gamble and Dr. William M. Wallace, Boston.

In this paper data are presented to illustrate two obstacles to accurate measurement of balances for the individual electrolytes: the physiologic oscillation of balance, which produces wide differences in the day to day retentions of the extracellular electrolytes, and the insensible loss of electrolytes, for the direct measurement of which no practicable method is at hand. Methods of indirect estimation of the insensible losses in adults and in infants are considered and a few data obtained by direct but rough methods of measurement are presented.

DISCUSSION

Dr. Daniel C. Darrow, New Haven, Conn.: I am perhaps not quite as discouraged about the possibility of determining the losses of electrolytes as Dr. Gamble is. Dr. Edward L. Pratt and Dr. Robert E. Cooke and I have data on a few infants that give a reasonable picture of what we believe is actually happening. Dr. Cooke reported these results in the meeting of the Society for Pediatric Research, May 3, 1949, here in Atlantic City, N. J. I think, first of all, whenever possible, we shall have to do metabolic balance experiments under conditions that assure a minimal amount of sweating. In other words, the ideal condition would be to determine balances at 80 to 82 F. on patients without any clothing. Clothing confuses the picture, because we do not know for certain the exact temperature of the body. Second, with that method, we can apply the corrections in some such way as Dr. Gamble has. The other method is, of course, the one that we are trying, which is actually to wash the babies before the onset of a metabolic balance period and at the end. One has no assurance, in those circumstances, that one does get all the electrolytes, but we feel we are approaching this quite closely.

The fascination of doing balance experiments probably comes largely from our pleasure, as Dr. Gamble calls it, when we present a pretty picture. I think that workers will continue to try these difficult experiments.

Dr. Harry H. Gordon, Denver: Some years ago, my colleagues and I had an opportunity to study the excretion of electrolytes through the skin. At that time, Dr. P. H. Lavietes and Dr. J. P. Peters, of New Haven, Conn., were in sharp disagreement with Dr. L. H. Newburgh, of Ann Arbor, Mich., concerning the relative value of the metabolic (organic) and electrolytic (inorganic) methods of estimating water balance. We were able to obtain good agreement between results of the two methods in measuring the water exchange of premature infants whenever we could keep perspiration at a minimum. The infants were kept in a room of constant temperature and humidity, and the vasti test, which Dr. Levine had called to our attention, was used as an index of perspiration. As a measure of chloride excretion a piece of filter paper was applied to the forehead of the infant for sixty seconds, three times daily, and then exposed to silver nitrate and sunlight. Whenever the test gave a positive reaction, the room temperature was lowered or clothing removed to prevent appreciable unmeasured loss of minerals through the skin.

Prevention and Control of Infection in Nurseries for Premature Infants. Dr. Stewart H. Clifford, Boston.

The prevention and control of infection in prematurely born infants in nurseries that are part of a general children's hospital, where patients are admitted from "outside," is an entirely different problem from that in nurseries of an obstetric unit where all infants come directly from the hospital's own delivery room.

Vital statistics from the Boston Lying-in Hospital give the proportion of premature infants to be expected in the various groups according to weight at birth, together with the mortality rates for each group. Ninety-six per cent of all deaths of premature infants at the hospital occur during the first week of life. Infection is not a problem because all infants admitted are "clean" and because the "Standards and Recommendations for the Hospital Care of Newborn Infants—Fullterm and Premature" of the American Academy of Pediatrics is rigidly followed.

Vital statistics from the nursery for premature infants at Infants' Hospital show its population to be highly selected. More small premature infants and fewer large ones are admitted for care there than at Boston Lying-in Hospital. The larger infants have a higher mortality rate than the Boston Lying-in group, as would be expected since only the problem babies of this weight are sent in to the Infants' Hospital. The smaller infants experienced a much higher mortality than should be expected due to infection. Infection is revealed as the problem of paramount importance in the nursery for premature infants at the Infants' Hospital.

The methods recommended for the prevention and control of infection in nurseries for premature infants are:

1. One physician should be placed in charge and be made responsible for the service in nurseries for premature infants.

2. "Standards and Recommendations for the Hospital Care of Newborn Infants —Fullterm and Premature" should be followed in detail.

3. Nurseries for premature infants in obstetric hospitals should not admit patients delivered outside.

4. Nurseries for premature infants in pediatric hospitals should campaign to have the infants admitted as soon after birth as possible. No baby older than 7 days of age should be admitted.

5. The nursery for premature infants should be located as far from areas in the hospital where sick infants cared for as possible.

6. The nursery for premature infants should be constructed or reconstructed with as many barriers between it and the rest of the hospital as practical. Entrance to the nursery should be gained through an anteroom.

7. Members of the medical and nursing staff while caring for premature infants should be relieved of all duties involving the care of sick patients.

8. Ideally, every infant should be kept in his own completely enclosed and air-conditioned unit from his admission to his discharge from the hospital.

9. All formulas should be terminally sterilized either by steam under pressure or by the flowing steam method.

10. In nurseries for premature infants outside obstetric hospitals, all infants admitted, with the possible exception of healthy newborn infants, should be given a prophylactic course of treatment with penicillin and sulfadiazine.

The vital statistics from the nursery for premature infants of the Infants' Hospital for 1948 show a dramatic reduction in mortality for all infants weighing 4 pounds 6 ounces (2,000 Gm.) or less. All deaths of premature infants in 1948 took place within the first five days of life. With 106 infants admitted to the nursery for premature infants in this hospital in 1944, there were 35 who received 336 individual clyses, intravenous injections, transfusions or plasma infusions. With 94 admitted to the same nursery in 1948, there was not a single such treatment given.

Infection in nurseries for premature infants can be prevented and controlled.

DISCUSSION

DR. CHARLES H. SMITH, New Brunswick, N. J.: Those of you who work under university hospital conditions can not realize, perhaps, the appalling status of the premature infant away from medical centers. I observed the care given in one good, well managed unit for premature infants, and in several hospitals where a premature infant was a rare accident and where there was no setup for their care. I think Dr. Clifford's observation of the importance of a good isolation incubator is, for the large part, a most appropriate solution.

One of the points of procedure done badly in so many places is the nipple technic: The nurse who changes the diapers puts the nipple on the baby's bottle. That is done to an extent which, I imagine, few of you can realize.

I have always felt that the avoidance of chilling was an important factor in keeping up the child's resistance against infection. Chilling is one of the dangers to a newborn infant, but is it not possible that the premature infant in an incubator is also subject to chilling when his clothing is not properly kept over him? There is a differential between the premature infant's idea of normal temperature and the temperature of the incubator of 10 or 15 degrees (F.). He, being poorly insulated, can lose heat even when he is in an atmosphere somewhat warmer than the ordinary atmosphere of the nursery.

My associates and I observed, a year or two ago, that it was easier to keep the premature infant's temperature stable in an incubator when he was wrapped in a light sleeping blanket than when he was allowed to lie half-naked with the classic splitback nightgown which so many of them kick off.

Perhaps the gravest danger to the child in the outlying hospital is the food he is given. It is not a rare thing to see an obstetrician, if he has the privilege of ordering food, give a premature baby a formula which contains three times as much food as he can possibly handle. It seems to me that nipple technic, chilling and too much to eat are the greatest factors in lowering a child's resistance to the infections he will get if he can.

DR. JAMES MARVIN BATY, Brookline, Mass.: My associates and I had a smaller experience in an almost identical setup at the Boston Floating Hospital, which is not too far distant in miles from the Children's Hospital. Our premature infants showed a like incidence of secondary infections and increased mortality. About a year ago, we instituted a similar change in physical setup, except that we did not use, and do not use, the individual isolated units. We were able to separate our nursery, physically, by moving it to a different floor from that housing the sick infants. Since the new nursery was opened, we have had 29 infants; we have had no deaths in those over the age of 2 weeks and no intercurrent infections, although the circumstances are otherwise identical.

I think it is important that we also instituted a method of terminal sterilization in preparation of formulas similar to that Dr. Clifford mentioned was instituted at the Children's Hospital at almost the identical time, so that the faulty nipple technic Dr. Smith mentioned is corrected. The formulas are prepared; the units are assembled, covered and sterilized. At feeding time the nurse simply removes the outside covering and feeds the infant; the nipple does not have to be touched.

DR. JULIAN D. BOYD, Iowa City: When a physician makes a survey of the factors which may be involved in infections in the nursery, he must neglect nothing, and sometimes he encounters factors he never would suspect. A year or two ago, we had an epidemic in our nursery. A careful survey was made. A stock solution of iron and ammonium citrate, used to supplement the infants' feedings, was found to be heavily contaminated with coliform organisms. It seemed probable that this solution had served to maintain the epidemic.

DR. HAROLD K. FABER, San Francisco: I should like to discuss one controversial point on which I have some information, the problem of the care of the nurse's hands. For many years, at Stanford University Hospital, simple washing without the use of a brush was the rule, the nurse being required to wash her hands with soap after handling each baby and before going to the next. About a year and a half ago, my associates and I checked on the bacterial population of the nurse's hands after this technic, which, I believe, is quite generally used. We were alarmed by the large number of coliform, as well as other organisms, including nonhemolytic streptococci, presumably of intestinal origin, under the nails and on the hands after washing.

We then investigated dipping solutions. I mention these with hesitation because the Committee on Fetus and Newborn of the American Academy of Pediatrics, in its proposed standard procedure, has advised against the use of hand dipping solutions. However, our department of bacteriology made some careful studies of the bacterial population of hands after dipping in benzalkonium (zephiran®) chloride solution. We discovered that dipping in 1:3,000 solution reduced the coliform population on the hands, including the scrapings from under the nails, to practically nothing. In fact, the solution was so effective that stool material dropped into the solution was promptly freed of the coliform organisms. We still found a few streptococci on the hands, but in such reduced numbers that it was necessary to use broth cultures for their detection. We have, therefore, contrary to the Academy's recommendations, adopted the method of dipping of the hands and arms, using deep receptacles. The nurses, before going into a given unit of the nursery, are required to wash their hands and arms in soap and water, then to rinse off the soap carefully. In the nursery itself they employ the dipping technic, as described, before handling each baby. We do not regard this as the ideal solution in all respects, but the nurses have had no dermatitis, and, on the whole, we have found the results quite satisfactory in the prevention of infections in the babies.

DR. MYRON E. WEGMAN, New Orleans: Dr. Clifford emphasized the difference between the baby who is clean, since he was born in the hospital, and the one who comes in from the outside. It seems to me that the baby who is born in the hospital is not quite as clean as we think it is. At Charity Hospital in New Orleans some years ago, a small epidemic of diarrhea in the newborn occurred which came from the mother to a child when the child was delivered in a clean delivery room under aseptic conditions.

It has been the impression of my colleagues and me—I am sorry we do not have figures to substantiate it—that we have had just as many infections arise in our "clean" nursery as in our "suspect" nursery, to which infants are admitted who come in from outside.

I do not want to be misunderstood in this. I do not mean for a moment to fail to endorse and applaud the various precautions in regard to cleanliness which Dr. Clifford has insisted on, and which Dr. Faber has seconded just now. I do want to say that perhaps it is a mistake for there to be any weakening of precautions in the unit which admits babies born in the hospital, because the danger is great there, too.

I am disturbed at Dr. Clifford's advocacy of routine treatment with penicillin and sulfadiazine for all babies. Would not more difficulty arise from that procedure in the long run? Would Dr. Clifford comment on the failure of any difference to exist in 1948 in the mortality rate of his group weighing 1,000 to 1,500 Gm.

and that of the group weighing 1,500 to 2,000 Gm.? Ordinarily, there is a fairly sharp distinction in the rates between these groups. Is this just a chance variation because of numbers?

DR. ARTHUR H. PARMELEE, Pacific Palisades, Calif.: Dr. Clifford's experience closely parallels that of my colleagues and me in Chicago's Cook County Hospital in its station for premature infants. I think Boston might profit by Chicago's experiences in making prematurity a "reportable disease." In Chicago all premature babies must be reported to the Health Department by telephone within an hour after they are born. A classification of all hospitals is maintained. If the hospital at which a baby is born prematurely does not have the proper facilities for taking care of it, the baby is immediately transferred to one of the units recognized as satisfactory by the Health Department. That procedure might obviate some of the difficulty of getting babies into the unit for premature infants at an early date. A vigorous head of the health department is needed for enforcement of the law, I might add.

Terminal sterilization, of course, is an important item in any nursery for newborn infants, and particularly in a unit for premature babies. I think it deserves primary consideration. Another factor that I have found important in long experience with nurseries for newborn and premature infants is the constancy of the nursing personnel. If the head of the department likes her job and makes it attractive for the nurses who work with her, if the department is a loyal, constant one and if it is not used for teaching purposes (that is, with student nurses coming in for a short time and then disappearing), I think there will be an enormous improvement in the mortality statistics in both the full term newborn and the premature infant.

In regard to Dr. Clifford's statistics concerning the bacteriologists' showing such a high percentage of colon bacillus infection, we found that to be true also. We had a system of questioning every mother who came in in labor about her health, particularly about respiratory and gastrointestinal infections. Those mothers who had any illness of this category were put into a ward separate from that for the regular obstetric patients; their infants were taken to an entirely separate nursery and were not sent to be breast fed, so that they had no contact with the mother after birth. That policy greatly lowered our incidence of certain types of infection, and particularly colon bacillus infections, which so often cause meningitis or some other form of sepsis of the newborn.

DR. HARRY H. GORDON, Denver: My associates and I have had to wrestle with essentially the same problems that Dr. Clifford has mentioned, namely, to take care both of premature infants born in our hospital and of babies admitted from the ouside. Because the chief of our obstetric service, Dr. Stewart Taylor, has learned from Dr. Weymuller and Dr. Beck, of Long Island College of Medicine, Brooklyn, to trust pediatricians, we have been able to combine the facilities into one unit of twenty beds. That unit is, however, split into four parts: a two bed nursery for observation of infants admitted from outside, an eight bed nursery for infants requiring highly specialized care, an eight bed nursery for infants who are being prepared for discharge from the hospital and a two bed nursery for infants suspected of infectious illness.

Our plea is for some space to which a baby can be transferred for care when one is not sure whether he is sick or not, e. g., with the first one or two loose stools or with a disturbance in respiration that may be the beginning of a respiratory illness, and that he be removed completely from the unit for premature infants and sent to the pediatric service as soon as his illness is definitely diagnosed as one which may spread to other infants.

I should like to take exception to the data on the last slide that Dr. Clifford showed, if it implies that deaths due to infections decreased because of cessation of the use of fluids parenterally. In agreement with Dr. Clifford, we use sulfadiazine and antibiotic drugs freely. We have had about 200 admissions, half of them from the outside, with only 2 deaths after the first week of life. One was due to pneumonia, and 1 baby died immediately after an easy venipuncture and withdrawal of 5 cc. of blood.

DR. CHARLES A. JANEWAY, Boston: Part of these encouraging results—and I think a considerable part—is due to what I like to call medical engineering. There are few medical engineers, but one is a member of this Society, Dr. C. C. Chapple, of Philadelphia. It is Dr. Chapple's type of incubator that has made it possible to take care not only of this group of babies in the nursery for premature infants, of the hospital, but also of a number of surgical patients who come into the wards for treatment of congenital defects. The risk of contracting infection, with resultant morbidity or mortality, is run in all children's hospitals.

I should also like to stress the fact that this is an approach to the problem of the premature baby which makes it possible to work out the principles of prevention of cross infection. There is a tremendous amount of cross infection today in the wards of hospitals where sick babies are gathered together, a condition which has not been adequately appreciated in the past and which we still have to control.

DR. SAMUEL Z. LEVINE, New York: One source of infection was encountered as the result of careful autopsy examinations by Dr. Samuel W. Dooley, New York. In some of the children who died shortly after birth, he found Aerobacter aerogenes in the lungs. That organism is not sensitive to penicillin or sulfadiazine. If diagnostic punctures of the lung confirm this as an actual finding in vivo, one might consider the possibility of using streptomycin to reduce further the mortality from infections in premature infants.

DR. STEWART H. CLIFFORD, Brookline, Mass.: The various discussers have helped to emphasize the vulnerability of the premature infant to infection and the innumerable avenues by which infection can reach these infants. I had no intention of implying that premature infants born and cared for in the same obstetric hospital were immune to infection. I do contend that under these conditions it is easier to protect the infant from exposure to infection than it is when an infant is brought in from the outside where infection may already have been acquired. I am as opposed as Dr. Wegman to the principle of wholesale antibiotic treatment for all babies; however, it has been our experience that once infection is established in a premature infant to the point of obvious clinical recognition the process may be too far advanced for successful treatment. It is for this reason that we try to determine at the moment the infant is admitted to the nursery whether he is potentially infected or not. None of the "clean" babies in our obstetric hospital nursery receives routine prophylactic treatment on admission unless infection in the mother is suspected. In contrast, all those admitted from outside who are over 3 days of age are regarded as potentially infected, and all infants with a history of possible infection or with any suspicious physical finding are routinely treated with penicillin and sulfadiazine. Further experience may modify this technic as outside hospitals improve their care of the premature infant; but at the moment I credit this routine as being the main factor in the reduction of mortality in premature infants due to infection.

Dr. Wegman requested comment on the fact that in 1948 in the nursery of Children's Hospital infants from 3 pounds 5 ounces to 4 pounds 6 ounces (1,501

to 2,000 Gm.) experienced a mortality of 21 per cent, while infants from 2 pounds 4 ounces to 3 pounds 4 ounces (1,001 to 1,500 Gm.) who would ordinarily be expected to experience a much higher mortality, actually had a rate of only 25 per cent. This is not a chance variation due to numbers, since there were 38 and 24 infants, respectively, in the two groups. The explanation, I believe, is in the selective character of the admissions to a nursery admitting babies exclusively from outside in contrast to the obstetric nursery. In our nursery at Boston Lying-in Hospital, 22 per cent of infants admitted weigh 1,501 to 2,000 Gm. and 10 per cent weigh 1,001 to 1,500 Gm.—this can be called the normal expected incidence of premature babies in these weight groups. At the nursery of Children's Hospital 41 per cent of those admitted weigh 1,501 to 2,000 Gm. while 29 per cent weight between 1,001 and 1,500 Gm. This means that the referring physicians and hospitals keep their larger babies and send us the small ones. It also means that many of the smaller babies who are in poor condition at birth die before they can reach our nursery. The smaller babies who are admitted to our nursery, therefore, represent the best risks of that group from the community with an excellent chance of survival, provided they can be protected from infection.

Along with Dr. Faber we found benzalkonium (zephiran®) chloride the best of the dipping solutions. All dips are fairly effective when fresh—the danger comes as they are used because soap and protein are added and then they become a culture medium.

Since 1937, premature birth has been reportable by law in Massachusetts in the same manner as in Chicago—however, as Dr. Parmelee intimates, we have found having a law on the books and actually having early admissions of our premature infants to be two different things.

I agree with Dr. Gordon completely in the need for "suspect" nurseries where babies in questionable condition can be watched for developments. It hardly need be stated that the decline in the use of fluids parenterally was because of the decline in the incidence of infection and, therefore, in the need for such therapy, and not vice versa.

Abnormalities in the Secretion of the Adrenal Cortex. Dr. W. C. Deamer and Dr. H. K. Silver, San Francisco.

The two commonest manifestations of adrenocortical hormone imbalance in infancy are adrenal cortical hypofunction (Addison's disease or its equivalent) and advanced maturity along masculine lines. These two manifestations are of more frequent occurrence than the better known Waterhouse-Friderichsen syndrome and may be found separately or together. The syndrome of advanced maturity shows the unusual picture of simultaneous deficiency of one cortical hormone (the salt and water-controlling hormone) and excess of another (the androgenic hormone or hormones).

Since the recent recognition of the clinical entity of congenital adrenal hypofunction of the addisonian type, an increasing number of reports of its occurrence have appeared. Although still imperfectly delineated, it appears that severe and often fatal forms, as well as mild and possibly temporary forms, are both of more frequent occurrence than was formerly realized. The severe conditions often simulate pyloric stenosis of infancy, and their early recognition is of great importance, since the initiation of proper therapy with electrolytes and hormones may well be life saving. In regard to androgenic hyperfunction, if one is alerted to the situation, early recognition of the true sex of female pseudohermaphrodites becomes more

likely, as well as recognition of the slowly progressive masculinization which these patients undergo. Less confusing, but equally interesting, is the precocious puberty which develops in boys with a like condition.

In addition to the demonstration of unusual advancement of body growth, bone age and genital size in patients of both sexes with this excess of adrenal androgenic hormone, considerable early information may come from the study of their urinary ketosteroid excretion, which is increased. Roentgenograms made with the presence of opaque material in the urogenital sinus are also useful in recognition of the pseudohermaphrodite.

New and promising tests for adrenal function have recently been described by Forsham, Thorn, Prunty and Hills (*J. Clin. Endocrinol.* **8**:15, 1948). In part, these relate to the degree of fall in blood eosinophil and lymphocyte counts within four hours of a single injection of pituitary adrenocorticotropic hormone. Failure to obtain a normal drop in the number of eosinophils and lymphocytes implies that the adrenal gland of the patient has not responded properly to stimulation by the adrenocorticotropic hormone. The results of this test in 3 patients with addisonian deficiency are reported.

The types of conditions discussed thus far are associated chiefly with bilateral congenital lesions of the adrenal gland. Somewhat similar clinical observations were made in patients with acquired adrenal tumors, some of which were operable. All these points are illustrated in a group of 9 patients with adrenal diseases, the cases of 6 of whom were examples of adrenal insufficiency. The tendency for congenital adrenocortical hypertrophy to be familial is revealed in several instances. One patient (who had congenital adrenal atrophy) came to postmortem examination and was one of the few human beings whose condition illustrated the effects of possible overtreatment with desoxycorticosterone.

Among the other points of especial interest that were derived from a study of these patients were that (1) in the cases of excess of androgen there may be a delay of several months to a year during which there is no precocious epiphysial development (advanced bone age), (2) early replacement treatment of these patients with adrenal insufficiency must be given in much larger doses than is necessary after control has been obtained, (3) the precocious bone age is not necessarily paralleled by a similar precocity of the eruption of either the deciduous or permanent teeth and (4) increased eosinophilia may be a helpful observation in the diagnosis of adrenal insufficiency.

DISCUSSION

DR. WILLIAM A. REILLY, Little Rock, Ark.: I should like to emphasize the familial recurrence of this extraordinary combination of, on the one hand, overproduction of the androgens and, on the other hand, lack of the steroid controlling water and salt metabolism. This paradox, as it were, might well occur in other endocrine glands. I think we all recognize this fact from the picture in the clinical syndromes of the pituitary. For the benefit of others interested in the aspect, I have been unable to detect any illness during pregnancy. It does not seem likely that an illness in the mother would account for this paradoxic situation, because, again, it is occasionally recurrent in subsequent offspring. Another interesting sign in these diseases of the adrenal cortex is the hyperplasia occurring after birth. The remark that the disease continues after one does everything conceivable is well stressed. The situation is much like that with toxic diffuse goiter before the evolution and development of thiourea derivatives and radioactive iodine. The cause of the condition is not taken away from the gland. Only remedial

work is being done. The same process occurs in this diseased adrenal cortex. The cause of continuation of physiopathologic changes in the adrenal cortical hyperplasia after partial surgical removal is something to which we shall have to give our attention.

DR. LAWSON WILKINS, Baltimore: The combination of congenital adrenal hyperplasia with this addisonian-like picture has been interesting to my associates and me. We, and I think almost all other workers, previously were inclined to believe that the adrenogenic function of the adrenal gland crowded out or suppressed the other activities of the adrenal cortex which control electrolyte and carbohydrate metabolism. As was pointed out by Dr. Robert Klein, of Baltimore, there is much evidence accumulating that the process is not simply this, and that actually the adrenal glands are producing abnormal hormones or normal hormones in an abnormal ratio which may vary from patient to patient. In some patients these hormones cause loss rather than retention of salt.

The picture is different from that of a simple Addison's disease, in which Dr. Talbot has shown that there is uniformly low output of the 11-oxysteroids. These patients with the combined conditions, in our experience, have a normal or increased output of the 11-oxysteroids. Dr. Roger Lewis, of Baltimore, and Dr. Klein have tested a number of such patients with the administration of adrenocorticotropic hormone and have shown that stimulation of the adrenal gland with the hormones sometimes causes a diuresis of sodium and chloride.

Adrenocortical "Sugar-Fat-Nitrogen" Hormone as Measured by Urinary 11-17-Oxysteroid-like Substances and by Counts of Circulating Eosinophils. DR. C. URIBE R., A. S. ZYGMUNTOWICZ, M. WOOD, E. CHRISTO and DR. N. B. TALBOT, Boston.

This paper deals with that type of adrenocortical hormone which inhibits utilization of sugar, aids in the mobilization of body fat, favors gluconeogenesis from protein and prompts lysis of lymphoid tissues and eosinopenia. With the possible exception of very young infants, the rate of production of this hormone as indicated by the urinary "11-17-oxycorticosteroid" output per square meter of body surface per day is essentially the same (the range is 0.05 to 0.22 mg.) in all healthy persons regardless of size or sex. In early infancy the values may be lower. In panhypopituitary and hypoadrenocortical children and adults, the output tends to be abnormally low. By contrast, in endocrinologically normal pediatric and adult patients acute illness prompts a physiologic increase in 11-17-oxycorticosteroid values to levels (0.212 to 0.78 mg. per square meter of body surface per day) comparable to those observed in patients with pathologic hyperadrenocorticism of the Cushing's syndrome type (0.212 to 0.78 mg. per square meter of body surface per day).

Data on eosinophil counts are in keeping with these observations. With the exception of young infants, the blood eosinophils of healthy, nonallergic persons number between 100 and 350 per cubic millimeter, regardless of age or sex. The values found for newborn infants are much higher (the range is 150 to about 1,000 cells per cubic millimeter). Normally, the eosinophil counts of newborn infants fall gradually to adult levels within a month or so. Infants under 1 month of age if traumatized are apt to have relative eosinopenia (50 to 100 cells per cubic millimeter). In older infants and in children and adults, acute stress is apt within four to eight hours to result in absolute eosinopenia (0 to 50 cells per cubic millimeter).

To gain further information concerning ability to produce 11-17-oxycorticosteroids under conditions of stress, an epinephrine-eosinophil test was employed. Epinephrine normally causes release of pituitary adrenocorticotropin. This normally stimulates the excretion of 11-17-oxycorticosteroids which induce eosinopenia. In the test, initially, and sometimes again in four hours, about 0.3 mg. of epinephrine is given per square meter of body area subcutaneously. In most normal, nonallergic patients the eosinophil count falls to 50 or less within four hours after the first or second dose. When the pituitary or adrenal cortices are exhausted or destroyed, the count is apt to remain above 50.

These observations suggest the following conclusions: With the possible exception of very young infants, the normal rate of production of 11-17-oxycorticosteroids appears to be proportional to surface area. Though young infants may be hypoadrenocortical relative to older persons, there is no evidence that they suffer thereby. Under conditions of stress, endocrinologically normal pediatric patients produce 11-17-oxycorticosteroids in increased amounts. This causes eosinopenia and may explain such other phenomena as lymphoid involution and glycosuria. Some information concerning the functional integrity of the anterior lobe of the pituitary and adrenal cortices may be had by the restults of the epinephrine-eosinophil test.

DISCUSSION

DR. PAUL GYÖRGY, Philadelphia: During the last three years, in collaboration with Dr. Venning, of McGill University, Montreal, Canada, I have been conducting studies of this type. Our results, based on the reactions of the biologic glycogen test, corroborate completely the findings obtained by Dr. Talbot's chemical method. We found in newborn infants an excretion of cortin, in relation to surface area, probably comparable to excretions by adults.

Our studies were stimulated by an attractive but erroneous assumption that the catabolic S hormone in the mother will catabolize protein and a grading from the mother to the fetus should be established because of low production of the hormone in the fetus. Our results and those of Dr. Talbot obviate this assumption.

More recently, Dr. Joseph Medoff and Dr. Barbero studied in our department the fluctuation of eosinophil count in newborn infants during the first week of life. In many instances the eosinophil count after birth was found to be low, followed by sudden quick rise. This phenomenon may be connected, as Dr. Talbot pointed out, with the stress during labor and "rebound" after birth, when suddenly the newborn infant is without the stimulant previously furnished by the maternal adrenal glands.

DR. WILLIAM C. DEAMER, San Francisco: The value of shifts in the eosinophil count after administration of adrenocorticotropic hormone in arriving at an opinion on the status of the adrenal glands has been pointed out by Dr. Talbot. To 3 of the patients I have just presented, we gave adrenocorticotropic hormone and failed to get a 50 per cent drop in total eosinophil count, such as is seen in the normal persons. The adrenal deficiency these patients had was thus demonstrated.

A variation on this theme may have been shown by 2 of these patients. The one who had no adrenal tissue on one side and only a fragment on the other had several blood counts which showed an eosinophilia, the count varying from 17 to 24 per cent. The other patient showed 9 per cent eosinophils. Besides these 2 patients, there have been other patients with adrenocortical deficiency who have shown an eosinophilia. It is our impression that eosinophilia may be of diagnostic value in the recognition of adrenocortical insufficiency.

Developmental Aspect of the Child's Vision. Dr. Arnold Gesell, New Haven, Conn.

The camera concept of the adult human eye has so much truth and tradition in its favor that it has tended to obscure certain characteristics of vision peculiar to infancy and childhood. The development of vision in the individual child is complex because it took countless ages of evolution in the race to bring vision to its present advanced state. Human visual perception ranks with speech in complexity and passes through comparable developmental phases. The child's vision is never simply a reduced version of adult vision; nor is seeing a separate isolable function: it is profoundly integrated with the total action system of the child—his posture, his manual skills and coordination, intelligence and even his personality makeup. Vision is so intimately identified with the whole child that one cannot understand its economy and its hygiene without investigating the whole child.

Vision, therefore, may become a key to a fuller understanding of the nature and the needs of the individual child. In this sense, it has certain implications for pediatrics. The child sees with his whole being. Ocular care involves child care. The conservation of vision, particularly in the young child, goes far beyond the detection and correction of refractive error. Acuity is only one aspect of the economy of vision. From the standpoint of a developmental optics, there are several distinguishable functions which do not, however, operate as specific and fixed entities. These functions undergo growth changes correlated with the three primary neuroembryologic divisions, namely: (*a*) skeletal (fixation functions), (*b*) visceral (focus functions) and (*c*) cortical (fusion and interpretative functions). Some of these developmental phenomena have been under study at the Yale Clinic of Child Development.

In the course of individual development, gradients of performance are built up concurrently in all three of the fundamental functional fields. The various levels of these multiplying gradients are interwoven in an intricate but progressive manner. Accordingly, each age of infancy and childhood affords a distinctive picture of visual behavior more or less characteristic of its stage of maturity. Four factors enter into the developmental organization as follows: (1) coordination, the correlation of the two eyes conjugately and disjunctively; (2) reach, the distance at which the visual system operates; (3) scope, the relative salients of central and peripheral areas in a plane of regard (central versus peripheral), and (4) drift, the developmental drift or growth trends of the visual system as manifested by various functional indexes. A chart is shown to demonstrate the way in which the foregoing functional complex of the visual system influences the symptomatologies of visual behavior—normal and deviant.

DISCUSSION

Dr. Gertrud Reyersbach, Boston: Dr. Gesell has pointed out that seeing is profoundly integrated with the total action system of the child. My colleagues and I had an opportunity to document this in the children's medical service of the Massachusetts General Hospital in studying a large group of prematurely born children who were blind because of retrolental fibroplasia. I should like to speak only about several of the observations we made on the group of totally blind but mentally competent children.

There were approximately 75 children in the group. Pronounced retardation in motor development was observed in these children as a group. They were particularly late in learning to walk. Speech was delayed but less seriously so than

the motor development. They gagged on chopped foods, and they had a hard time learning to chew. In many of them, the sleep pattern was reversed: They were awake during the night and slept during the day. At one time or another, in the early years of life, each of the children showed one or more of the following signs: head banging, head rolling, swaying, rubbing of the eyes, temper tantrums and humming. Many of the children would not hold their heads up.

Furthermore, it was noted that many of these children had attained an achievement, such as walking or talking, and then, after a while, stopped the activity and for months neither talked nor walked. This regression, which was often interpreted as mental inadequacy, appeared proportional to lack of contact with their environment. When efforts were made in the hospital by psychiatrists or in the home by instruction to parents, the children responded by resuming normal developmental behavior and diminishing the use of "blindisms" as an outlet for tensions. These observations indicate the importance not only of considering the total action system of the child but also of providing to blind infants adequate contact with their environment.

DR. ARNOLD GESELL, New Haven, Conn.: I have made no observations that have a significant bearing. I think the possible differences in postconceptional age are so great that they tend to show themselves in variations in the foveal picture. I wish I could say more.

Mercury in the Urine of Children with Acrodynia. DR. JOSEF WARKANY and DONALD M. HUBBARD, Cincinnati.

Infantile acrodynia was given much attention by pediatricians between 1920 and 1945. In recent years its incidence has apparently declined in this country, but it still represents a serious medical problem in other parts of the world. The symptoms of acrodynia became well recognized, but the causation remained obscure. Infectious, postinfectious, nutritional, endocrine and toxic theories have been advanced. Of these, the toxic theory had much in its favor and arsenic was suspected by many as the etiologic agent. In fact, chronic arsenic poisoning has many symptoms in common with acrodynia: Muscular weakness, burning pain in the extremities, anorexia, stomatitis, conjunctivitis, lacrimation, perspiration, dermatitis, desquamation and alopecia occur in chronic arsenic poisoning. We, therefore, submitted in the past samples of blood and urine of several patients with acrodynia to the Kettering Laboratory of Applied Physiology, in Cincinnati, with the request to search for arsenic, but excessive amounts were never found. In April 1945, another patient with typical acrodynia was admitted to the Children's Hospital of Cincinnati and specimens of blood and urine were sent again to the Kettering Laboratory. That time we asked more generally for "qualitative metal determination," hoping that another metal might be discovered. The blood was analyzed spectroscopically and its content of lead, tin, aluminum, copper, manganese and silver was found to be normal. Antimony, cadmium, cobalt and thallium were absent. In the urine, lead, tin, aluminum, copper, manganese, silver, arsenic, antimony, cobalt, thallium and cadmium were absent. A quantitative determination of mercury was done in the urine by Hubbard's photometric method, with the use of di-beta-naphthylthiocarbazone as a reagent, and 360 micrograms per liter was found. Since this is a large amount of mercury to be excreted, an amount comparable to that found in persons with industrial mercury poisoning, another specimen was examined and 320 micrograms per liter was found. Thus, it was established that this child with acrodynia excreted large amounts of mercury, but the source of mercury could not be ascertained. Since 1945, the urine of 31

children with acrodynia was examined for mercury. Ten of these children were seen in Cincinnati and 21 in various other cities of the United States. We are indebted to the pediatricians of these children for sending us the specimens of urine, as well as abstracts of the case histories. At the same time determinations of mercury were done on the urine of 59 control subjects.

In the table the values for mercury found in the first determination on the urine of children whose condition was diagnosed as acrodynia are compared with those on that of the controls. Mercury was found in 29 samples from the acrodynic children and only 2 were free of it. In 50 of 59 control persons (or about 85 per cent) no mercury was detected in the urine. Of the 8 controls listed in the column "1 to 50 micrograms" 3 had low values, which were within the limit of error of the method. In 3 control children in whose urine small amounts of mercury were found in the first sample, none, or minimal amounts, was found in subsequent samples, so that contamination of the first sample could not be excluded. One control child actually excreted mercury. We were able to contact his physician

Mercury Content of First Urinary Specimens of Patients with Acrodynia and of Controls

Mercury in Urine, Micrograms per Liter	Number of Persons	
	Patients with Acrodynia	Controls
More than 400	3	0
301 to 400	3	0
201 to 300	7	0
101 to 200	4	0
51 to 100	6	1
1 to 50	6	8
0	2	50
Total	31	59

and were told that the child had received calomel (mild mercurous chloride U. S. P.) tablets from him. The fact that a child who was given calomel and excreted mercury in measurable amounts was free of symptoms of acrodynia is of importance and will be discussed later.

Twenty-nine children with acrodynia were under 4 years of age and, thus, showed the age incidence characteristic of the disease. Two children were older, 8 and 13 years of age, respectively. These were the children in whom no mercury was found. Their cases were atypical in other respects also. The 8 year old girl had had acrodynia-like symptoms for three years, when the determination of mercury in the urine was done. The 13 year old boy had had three attacks of acrodynia, the first at the age of 2½ years and the second when he was 5. Only at the time of his third attack was his urine examined for mercury and found to be free of it.

In the first cases of acrodynia that we examined the source of mercury excreted in the urine could not be ascertained. But recently, since we know what to ask for, the origin of the mercury excreted could be determined in the majority of cases. Calomel given in "teething powders" or worm cures was the most frequent source of mercury in patients with acrodynia. Ammoniated mercury ointment and mercury bichloride used for rinsing diapers accounted for some of the cases.

But there must be other sources, since in a few of our recent patients with acrodynia who excreted mercury in the urine any mercurial medication was denied in spite of thorough questioning.

The fact that mercury is excreted in the urine of so many children with acrodynia suggested that in small children a causal relationship may exist between exposure to and resorption of mercury and the symptom complex of acrodynia. At first, this theory appeared rather dubious, but recently many confirmations have been received from this country, England, Canada and France. Fanconi and his co-workers in Switzerland have observed many cases of acrodynia following mercurial medication, and in a number of their patients examination of the urine revealed excretion of mercury comparable to that of ours. The correlation between mercurial medication and acrodynia is the more striking as the dispensation of mercurial drugs has declined in recent years. Fanconi and Botsztejn reported in a recent paper that 19 of 20 children with acrodynia seen in Zurich during the past eighteen months had been treated with mercury shortly before onset of the disease.

The chief objection to the theory of the mercurial origin of acrodynia was the fact that thousands of persons are treated with drugs containing mercury, while only few acquire acrodynia. We have mentioned that one of our control patients who did not have acrodynia had received calomel and excreted mercury in the urine. Similarly, mercury was found in the urine of a number of healthy children and adults with known exposure to mercury. This fact suggests that an individual susceptibility to mercury intoxication exists in children who have acrodynia. We do not know the factors which determine the susceptibility, but age is obviously one of them. Infants over 6 months and small children up to 4 years of age are more likely to show acrodynia following administration of mercury than older children and adults.

It is likely that some of the symptoms of acrodynia can occur without exposure to mercury. Arsenic, ergot, ustilago and other toxic substances are known to produce symptoms which partly resemble those of acrodynia. However, in a small child with the symptom complex of acrodynia mercury should be suspected as the causative agent first.

Bivings and Lewis suggested treating acrodynia with BAL, since this medicament has been used successfully in treatment of heavy metal poisoning. We have not had sufficient experience with this drug in the treatment of acrodynia to venture judgment. In some of the cases of our series, rapid recovery following treatment with BAL was reported by the physician. In others, the results were disappointing. Two patients died in spite of BAL treatment and in 2 patients shocklike incidents occurred during the treatment.

It seems to us that prevention of acrodynia is possible and preferable to treatment. Teething powders, the most frequent cause of acrodynia in our series, are apparently completely useless and should be eliminated. Santonin and calomel tablets can be replaced as a vermifuge by other drugs in small children. Nonmercurial disinfectants and bactericidal ointments are available. Thus, it should not be difficult to prevent those cases of acrodynia which are due to mercurial medication.

DISCUSSION

DR. MURRAY H. BASS, New York: From what we have heard from Dr. Warkany and from others in various parts of the world, it does seem that many cases of what we call acrodynia apparently are due to mercury. One of the important points is that cures have been established by the use of BAL. I should

like to call attention to the fact that mercury can cause many different types of pathologic pictures in children. This group of symptoms is unique and in typical mercury poisoning, which occurred when mercury was used particularly for syphilis, salivation and other symptoms are the chief evidence of intoxication. The children who are sensitive to mercury have an entirely different set of symptoms. This group has interested me—and I have reported a number of cases of various types of sensitization in children. A child can get a rash similar to that of measles or one that looks like erysipelas. We had one child treated for virulent scarlet fever, who looked as though she had been badly burned. She was unconscious, with a temperature of 106 F. She had been treated with ammoniated mercury for chickenpox. It is extremely difficult at times to tell how mercury reaches the patient. Dr. Warkany's statement about trying to find these various sources applies also to the problem of mercury sensitivity. One must not give up when one suspects this condition but try to find every possible way in which mercury may reach the child. One child had severe symptoms from simply handling a glass funnel in a laboratory through which someone had previously poured mercury. This child had had serious symptoms before that incident, and so we knew she was sensitive to mercury. One child had urticaria which could not be explained, until we found it was due to amalgam fillings in her teeth, and when they were removed her difficulties cleared. When the dentist removed the amalgam, the child's temperature rose to 102 F. and her feet swelled so that she could not put shoes on. Mercury sensitivity can cause symptoms in children which are completely unrelated and different, and, if, as it seems, acrodynia is due to mercury, there must be some second factor in these children that causes this particular symptom complex.

DR. JULIAN D. BOYD, Iowa City: This past winter a child with acrodynia was referred to me by a pediatrician. With the usual methods of treatment, the child did not improve under our care. Thinking of the possibility of mercury poisoning, I had a pooled specimen of urine analyzed for that metal, but none was found. The patient was returned to the care of the referring physician. Despite the negative urinalysis, the pediatrician instituted BAL therapy, and the child's symptoms subsided promptly. From Dr. Warkany's presentation, one must conclude that this child may have had sensitization to and poisoning from mercury, even though none could be recovered from the urine.

DR. A. ASHLEY WEECH, Cincinnati: Dr. Warkany, would you tell this group of pediatricians how physicians use teething powders?

DR. ROGER L. J. KENNEDY, Rochester, Minn.: My colleagues and I have been interested for some time in the study of the pathologic aspects of this disease in infants. As you know, there is not much agreement among those who have had an opportunity to study this condition. For some time there has been interest in methods of reproducing the condition in animals, which, so far as I know, have been unsuccessful.

Would Dr. Warkany tell us what his thoughts have been in respect to the use of mercury in animals in an effort to reproduce the condition, so that workers might have an abundance of material to study histopathologically?

DR. JOSEPH B. BILDERBACK, Portland, Ore.: At long last we may have a specific for acrodynia. I feel that Dr. Warkany and Mr. Hubbard deserve great credit for discovering that the urine of children with acrodynia contains mercury and that of the controls does not. Dr. Warkany told me some years ago that he had found mercury in the urine of children and was wondering about it as a

cause of acrodynia. I said facetiously, "Josef, we have eleven reasons now for acrodynia, and yours will make twelve; that makes it an even dozen, and I thank you." But I did nothing about it.

For a long time, poisoning by heavy metals, particularly arsenic, had been considered as a possible cause of acrodynia but it had never been proved. Dr. Lee Bivings, of Atlanta, Ga., was informed that Dr. Warkany and Mr. Hubbard had found mercury repeatedly in the urine of children with acrodynia. Dr. Bivings knew that BAL was used successfully in the treatment of poisoning with mercury bichloride and, having at that time a patient with acrodynia, he used BAL for treatment. The child had a history of receiving, a few weeks earlier, powders containing calomel. The child's condition responded rapidly to BAL and he was almost well within a month. During the last two years, Dr. Bivings has treated several other patients having acrodynia with BAL and has accumulated the reports of physicians throughout the world who have used the drug in its treatment, most of them with brilliant results.

Formerly, the disease lasted from six to twelve months and, while there still may be some loose ends that we do not understand, it will take the acid test of time for us to know whether BAL is the full and final answer. However, I feel that anyone having a patient with acrodynia would be justified in using BAL as in the past we have had no intelligent treatment for the disease. It is felt that the symptoms of acrodynia are not those of acute mercurial poisoning but those of a sensitization or an idiosyncrasy to mercury. Mercury in the form of calomel in worm or teething powders or as gray powder (mercury with chalk U. S. P.) is given to thousands of children but only rarely does a child have the symptoms of acrodynia. Australia has a great many cases of a disorder that is known as Swift's disease or pink disease (erythredema polyneuropathy). One clinician reported 150 cases seen within a few years. Mercurial compounds are used excessively in Australia, particularly in the treatment of children. This may account for the increased incidence.

I feel that Dr. Warkany has made a valuable discovery in finding mercury in the urine of children with acrodynia and none in the controls. Dr. Lee Bivings deserves great credit for being the first physician to use BAL to relieve symptoms of this apparent sensitization to mercury. He has used the rare gift of imagination in the application of knowledge. There is enough glory for all: for Warkany for finding the mercury and for Bivings for using BAL.

Dr. S. Graham Ross, Montreal, Canada: Has Dr. Warkany observed any cases of mercurialism in infants without the skin eruptions characteristic of acrodynia. Recently, we had a case of an infant in a hospital who, with a condition at first undiagnosed and without the typical skin eruptions and involvement of the extremities seen in acrodynia, was found to have an excessive amount of mercury in the urine. The child's disorder responded in a fairly satisfactory manner to treatment with BAL. It would be of interest to observe in the future the number of cases of this type that occur which do not show the acrodynia-like picture. Another observation was made in the case of a child who was admitted to the hospital with a diagnosis of diabetes. He had a typical attack of acrodynia, with renal glycosuria. He also showed an excess of mercury in the urine. The glycosuria disappeared while he was under treatment with BAL.

Dr. Arild E. Hansen, Galveston, Texas: Is there any relation between the content of mercury in the urine and the onset of the disease, in other words, what is the time interval? We know that acrodynia is a disease that does not respond to various therapeutic agents, but some pediatricians might be tempted to use preparations in treatment which have mercury as one of the ingredients.

DR. J. C. SPENCE, Newcastle-on-Tyne, England: I should like to comment on the English experience with acrodynia. As you know, it is one of the backward countries which still continues use of mercurial drugs in high degree. My own clinic, with a high percentage of correct diagnosis, accumulated data on more than 800 cases that were carefully studied. In the search for a secondary factor, assuming it is mercury poisoning, that would explain the reason so few patients get it, such large statistically significant numbers indicate that there is a familial tendency in this disease. I found, recently, in Australia a paper read on the same subject. In my own experience, I have seen it in cousins and in the members of the same family, never at the same time—except in one set of circumstances in which twins had it. I have seen acrodynia come in families with 2 children who had an interval of two to eight years between them. It may be that the family has a familial habit of giving teething powder, if that be an explanation; there seems to be something in the person's susceptibility which is genetically determined. Has Dr. Warkany had an opportunity to elucidate this problem?

DR. JOSEF WARKANY, Cincinnati: Although the use of teething powders is widespread and has been customary for a long time, we learned only relatively recently of its existence. I am told that the powder is put in the child's mouth and rubbed on the gums; then the child swallows the powder. I may be wrong, since I have never seen an application of teething powders. It is of interest that there is much acrodynia in England, Australia and South Africa, countries where, I am told, teething powders are sold on a large scale.

Dr. Hansen has suggested that a child could have symptoms of acrodynia first and receive a mercurial preparation for their treatment later. That certainly could happen and we have considered this possibility throughout. In some cases the sequence of events was doubtful. In one, a child had a diaper rash and was treated by rinsing the diapers in a solution of mercury bichloride. Two weeks after the beginning of this procedure the child showed the typical symptoms of acrodynia. One could interpret the diaper rash as the first symptom of acrodynia and consider the treatment of the diapers as incidental. In 1922, Weber described a case of acrodynia with necrotic changes in a young child. The child had some skin lesions which were treated with many mercurial preparations. It is difficult to decide now whether the child had acrodynic symptoms before or only after the application of mercurial preparations. However, many children who were essentially well, to whom teething powders were given because of the child's "cutting teeth" and crying, showed the symptoms of acrodynia some time later. We have in our series a number of cases with few symptoms, such as restlessness and hypotonia, but no rash. "Formes frustes" of acrodynia occur and we may change our conceptions of the disease and include mild reactions to mercury in the term "acrodynia."

We have considered animal experiments and have thought of giving mercury to young rodents, especially to the mother who nurses her young. In this way mercurial compounds could be given to young animals in their infantile period of life.

We tested one specimen of urine of a child who had acrodynia-like symptoms after he obtained several amalgam fillings. The urine did not contain mercury. My urine was examined after I received an amalgam filling and several specimens were free of mercury. These observations do not exclude the possibility that some persons react to traces of mercury which are so small that their presence cannot be detected by urinalysis.

We know nothing about the predisposing factors of acrodynia. Dr. Spence has stated it is perhaps an inherent anomaly of the child. We have found histories of allergy in some, but not in all, case reports of our series. Not all patients had been asked specifically about this point. An allergic predisposition could explain the occasional familial occurrence of acrodynia; but the possibility of a "familial" use of teething powders, worm treatments or mercurial ointments should also be considered.

I wish to thank Dr. Bilderback for his remark made several years ago that we had discovered the twelfth cause of acrodynia. His statement was a great stimulus to us and we were honored by it. After all, it is relatively easy to find the first cause of a disease but rather difficult to discover the twelfth.

Mental Status of Children Who Have Recovered from Erythroblastosis Fetalis. Dr. Richard Day, Joan Gerver and Dr. Irene Shapiro, New York.

Most reports indicate that approximately 10 per cent of patients who have recovered from erythroblastosis fetalis manifest severe central nervous system disease, thought to be the result of kernicterus. It is generally believed that a patient either has kernicterus or entirely escapes involvement of the nervous system. If so, then this complication differs from the other manifestations of erythroblastosis, since the others show gradations from mild to severe.

The purpose of this research has been to investigate the mental state of the recovered children who do not have choreoathetosis, spasticity or obvious mental deficiency. We have also excluded from the study those cases in which the mother brought the child to us because of suspected defect. The children examined were called in because the hospital record showed that the subject had had well substantiated erythroblastosis fetalis immediately after birth. Only those children have been tested who were at least 2½ years old and who also had an older sibling without neonatal disease. Fifty-four such pairs of children have been found and given Stanford-Binet intelligence tests. The average intelligence quotients of the normal siblings was found to be 111 and that of the affected children, 101. Although a difference of this magnitude is not great when considering a single child, statistical analysis indicates that it is a real difference, the odds that it arises from chance alone being less than 1 in 1,000. Two steps have been taken to eliminate the possibility that the recovered children were handicapped in the test because of being younger than their normal siblings. A correlation between age and intelligence quotient was made in the case of the affected children and the controls, and none was found. Second, the same psychologist examined 16 pairs of children drawn at random from families who were free from erythroblastosis attending the outpatient department of Columbia-Presbyterian Hospital. In the case of this control group of families, the age spread was about four and one-half years, as was the case in the erythroblastotic families. Both the older and the younger members of this control group of families had an average intelligence quotient of 112.

Factors other than erythroblastosis which might have acted to depress the intelligence of the children that we have not been able to exclude as possibilities are unconscious bias on the part of the psychologist, parental attitudes to a child who has been ill and nonspecific influence of neonatal disease. It is concluded that there is a high degree of likelihood that many children who apparently made a good recovery from erythroblastosis fetalis have suffered minor degrees of mental impairment.

DISCUSSION

QUESTION: Is there any relationship between the form of treatment and the results of tests?

QUESTION: Was there any more prematurity among the group affected by this condition than among the other babies?

DR. RICHARD DAY, New York: None of these children was treated with replacement transfusions. We hope to make a similar analysis of those who have been so treated. The infants in the present series all received small transfusions. We could find no relationship between the incidence of kernicterus or the intelligence quotient and the apparent severity of the disease as measured by a criterion such as the amount of anemia or jaundice or the number of transfusions. Our data on the effect of prematurity on the intelligence quotient are not complete.

Further Observations on Kernicterus in Erythroblastosis Fetalis. DR. VICTOR C. VAUGHAN III, DR. FRED H. ALLEN JR. and DR. LOUIS K. DIAMOND, Boston.

Kernicterus is an acute disease of early neonatal life, occurring in about 10 per cent of infants with erythroblastosis fetalis and rarely, if ever, in those with other morbid states. Factors influencing morbidity are maternal anti-Rh titer, length of gestation and hereditary factors. There is no demonstrable relationship with the degree of anemia; the significance of this is not understood. The disproportion between extent of jaundice and degree of anemia suggests a relationship to hepatic function. Several different antibodies have been responsible.

The signs and symptoms of this disease have not been readily recognized in the past, although they are characteristic. These are described and illustrated. Ten to thirty per cent of babies with kernicterus survive the acute phase of the disease and show gross motor and, usually, gross mental retardation. An occasional child has shown a remarkable degree of recovery.

Postmortem studies show histologic changes in the neurons of the basal ganglions and other nuclear centers of the brain in about 60 per cent of cases. The lack of histologic change in the remainder is strong evidence that the disease is an acute one. Gross staining of the nuclei has not been observed in stillborn babies in our experience.

Prevention of prematurity may be one way to reduce the frequency of kernicterus. Artificial reduction of maternal titer is presumably equally important, and since the disease would appear theoretically preventable, continued efforts must be directed to treatment in the first days of life. A decrease in the incidence of kernicterus following exchange transfusion has occurred, but this cannot be shown with statistical confidence to be due to the fact that exchange transfusion has been used. It is at present more likely that measures directed at prevention of immaturity are responsible for this decreased incidence.

The tables and figures shown were derived from a study of more than 300 cases of erythroblastosis fetalis observed at the Children's Medical Center and The Boston Lying-in Hospital during the last four years.

DISCUSSION

DR. SAMUEL LIVINGSTON, Baltimore: Were any of these patients followed with the electroencephalograph? I think the electroencephalogram would act as a good prognostic guide. If pathologic tracings persisted, then one could speculate that the patient would be mentally retarded or would display epilepsy later in life.

DR. PAUL GYÖRGY, Philadelphia: Some of us, like Dr. Leonard Parsons, in Birmingham, England, and, apparently, Dr. Day and our own group in Philadelphia, feel that kernicterus is related to some type of hepatic injury of undetermined origin or quality. It is difficult to find evidence for this hepatic injury and for its pathogenesis.

One table that Dr. Allen presented, for the data on which he could not find any explanation, appears to me significant in this connection as circumstantial evidence, namely, the prevalence of boys among the patients with kernicterus. It interested me greatly, because I have made, during the last five years, the same observation in animals, even in sexually immature animals, with regard to nutritional hepatic injury. The incidence of hepatic, as well as of renal, injury under identical experimental conditions is higher in males than in females. Therefore, the question arises whether this prevalence of boys among the patients with kernicterus is not an indication of the hepatic injury for which we are looking.

DR. A. ASHLEY WEECH, Cincinnati: Did babies presenting these so-called practically pathognomonic symptoms have serum calcium determinations done at the time they were exhibiting the symptoms? Many of the symptoms, such as refusal to eat and vomiting, position of the hands during the Moro reflex, arm rigidity, irregular respiration and a tendency to bleed, have been observed in neonatal tetany.

DR. RANDOLPH K. BYERS, Boston: I want to comment on the point Dr. György brought up about the increased incidence in boys in the group of children showing brain damage. I have been much impressed with this increased incidence in children with brain damage from a number of different factors; in a group of 30 or 40 children with lead poisoning that Dr. Lord and I studied—I have forgotten the exact numbers—about 80 per cent of those with persistent brain damage were boys. In the children who reacted poorly to pertussis vaccine, resulting in encephalopathy, 12 of 15 were boys. In erythroblastosis also, the boys show more brain damage. I should like to know the explanation of this difference which keeps turning up among patients with brain disease early in life.

DR. ALFRED H. WASHBURN, Denver: A number of us seems to be interested in this slide showing the greater incidence in boys. I am not searching for anything complex as a cause. If one considers the fact that the length of gestation plays a significant part in the incidence of kernicterus, and if, instead of the duration of gestation, one considers the degree of maturity, then it is worth remembering that there are a number of pieces of evidence that males are less mature organisms than females at birth. If kernicterus is really, as I feel, so closely related to the degree of maturity that one can increase its incidence decidedly by precipitating delivery before the baby is mature, then I might hazard a guess that this sex difference is closely tied up with the degree of maturity of the organism. Females being more mature at birth than males, it is only natural to expect a higher incidence in males.

DR. RICHARD L. DAY, New York: The question of whether exchange transfusions exert an effect on kernicterus is an important one. It could be that the incidence is low enough that any improvement might not be statistically demonstrable. Dr. Allen mentioned that there is a familial tendency toward kernicterus, and I wonder whether, in his opinion, an analysis of this is possible. We have two families in which a previous child had had kernicterus. A subsequent child in each family had erythroblastosis. A replacement transfusion was given, and both children are normal.

DR. IRVINE MCQUARRIE, Minneapolis: I have heard no one speak of the new work by Carter on the Rh factor (*Am. J. Clin. Path.* **17**:646, 1947). She claims to have extracted a substance from Rh-positive cells which will bring down the titer in Rh-negative pregnant women at an early period when injected parenterally. Presumably, such a substance would prevent kernicterus or erythroblastosis in the baby, if it actually works.

Dr. J. W. Goldsmith, of our department of obstetrics, went early to Mrs. Carter's laboratory in Pittsburgh and acquired the technic. He is making and using this material. I have heard his preliminary report on a few patients treated with it. Some of them showed a decrease in the titer in a most remarkable way. The substance, according to Carter, is a comparatively simple sterol and can be used in large-sized doses, if necessary. Knowing that Dr. Diamond is well acquainted with work of this sort in the country through his connections with the Red Cross, I hope he will tell us about it in more detail. It appears to me, from the little I have heard of the phenomenon, that it is a most promising point of attack on this problem.

DR. LOUIS K. DIAMOND, Boston: First, in regard to convulsions possibly due to tetany, we have done repeated calcium studies on the infants who showed these symptoms since we began treatment by replacement transfusion. In giving so much sodium citrate, we feared, and in some cases we actually proved, development of calcium deficiency. None of the children with kernicterus that we have followed with calcium studies from the second to the fifth days of life has any evidence of hypocalcemia. Its presence should be excluded in all these patients, and we have tried to do so. We have made no observations on electroencephalography of patients in the first few days. We have made tracings on a few older patients and have found abnormalities which I cannot interpret. None of these patients has gone on to the development of typical epilepsy or convulsions.

We, of course, have been deeply interested in the studies of Mrs. Carter. In fact, two of us have been in Pittsburgh and have gone over her material statistically. We can find just as much variation in her small series of cases as in our series of a similar nature that we have followed without treatment.

The fact that it takes many months of injections of this nonspecific Wassermann-like substance to produce the type of changes recorded does not seem to suggest a specific reaction. To date, none of the evidence that we have seen, either from Minnesota or from Pittsburgh, has suggested that any specific effect can be expected from this nonspecific substance.

Effects on Certain Forms of Mental Retardation of Altering the Cerebral Blood Flow. DR. CLAUDE BECK, DR. CHARLES F. MCKHANN and DR. W. DEAN BELKNAP, Cleveland.

The hopeless outlook for improvement of cerebral damage resulting from injuries at birth or cerebral infections justifies efforts to seek rehabilitation of damaged cells so far as possible. An operative procedure to improve cerebral blood flow has yielded interesting results.

DISCUSSION

DR. IRVINE MCQUARRIE, Minneapolis: The demonstration is, I think, physiologically significant. That such a procedure may improve the function of the brain cells in the area which had previously been the focus of seizures cannot be denied. It would be interesting to know in a patient who responds satisfactorily

to methylphenylethyl hydantoin (mesantoin®), as this patient did, what type of physiologic changes are induced to cause relief of the disturbance.

DR. CHARLES F. MCKHANN, Cleveland: There are more questions regarding this procedure to which we do not know the answers than there are those to which we do know the answers. Someone has asked how long after injury the procedure can be carried out. The oldest patient on whom the operation has been done was a child 20 months of age with the injury dating from birth. I should like to emphasize the significance of the two sides of the neck as sites for the operation. In the early operations, the procedure was carried out exclusively on the right side, because we were dealing in most instances with cortical damage. However, there is no reason one cannot—and it is proposed in some cases where deeper brain injury may exist—perform the operation on the left side.

Another significant point is that if one does not like the results, the cross connection can be narrowed or closed. Thus, if anything untoward develops in these patients, and thus far nothing has, one can undo the procedure and reestablish essentially the situation as it was before, with the exception, of course, of the tied and severed jugular vein.

Anticonvulsive Property of Glycerin and Related Compounds. DR. LASLO KAJDI and DR. SAMUEL LIVINGSTON, Baltimore.

The ketogenic diet has been used with considerable success in the treatment of epilepsy in children. The chief physiologic effects of a ketogenic diet are (1) production of a mild degree of acidosis, (2) production of ketosis and (3) production of a mild degree of dehydration. It is known that each of these factors lessens the tendency to convulsions, and it is generally believed that the beneficial results of the ketogenic regimen are due mainly to a combination of all three of these factors. These three factors arise from the metabolism of the fatty acids contained in the diet.

We have felt that the acidosis, ketosis and dehydration are not the complete explanation of the mechanism of the ketogenic diet. In 1946, Dr. Einar Lundsguaard, of Copenhagen, Denmark, discussed the metabolism of glycerin at one of the meetings of the Johns Hopkins Hospital Medical Society. He reported that glycerin is metabolized in cats and human beings only in the liver, that it is converted in the liver into some unknown intermediate product and that this product is eventually utilized by the other tissues.

It has been shown also that in completely diabetic dogs all the glucose administered was excreted in the urine and all the glucose in the protein was liberated. Yet, the brain of these dogs continued to function, although the dog's physical condition went downhill rapidly. Since it is generally maintained that nerve cells metabolize only glucose, we felt it possible that the nerve tissues of these diabetic dogs obtained their carbohydrate fuel from the glycerin of the fats metabolized. The ketogenic diet, as prescribed in the treatment of epilepsy, contains about sixteen to twenty times as much glycerin as a normal diet. These facts prompted us to investigate the anticonvulsive properties of glycerin. Two children, whose frequent grand mal seizures and myoclonic jerks were inadequately controlled by the ketogenic diet, became free of the myoclonic jerks for several weeks when glycerin was added to their diet. This happened in spite of the fact that the diacetic acid and acetone reaction of the urine diminished and on some occasions was completely negative.

Glycerin was administered, in addition to their previous medication, to a group of 46 patients of the Epilepsy Clinic of the Johns Hopkins Hospital and the Perry

Point Veterans Administration Hospital. All these patients were on normal diets. There were 28 children and 18 adults. Seizures were controlled in 11 patients, significantly improved in 14, moderately improved in 5 and uninfluenced in 16. It seemed equally effective in those with grand mal and petit mal, in adults and children, but more effective in those with idiopathic than in those with organic epilepsy. No toxic effect was observed. We wish to emphasize that these results were also obtained when other anticonvulsive drugs were used in combination with glycerin. In rabbits, the convulsive threshold to metrazol® given intravenously was determined. Then the animals received by stomach tube 5 to 15 cc. of glycerin or propylene glycol.

It was found that the minimal protecting dose is 10 cc. of glycerin when given an hour before the metrazol®. It protected 50 per cent of the animals. Propylene glycol was not effective in a 10 cc. dose. However, 15 cc. given an hour before the metrazol® was given protected more than 80 per cent of the animals. According to the literature, isopropyl alcohol protected animals against metrazol® convulsions and against electric shock.

DISCUSSION

DR. IRVINE MCQUARRIE, Minneapolis: I have always calculated glycerin as antiketogenic, of course, and I am afraid that I have neglected that part of the ketogenic diet, if the authors are correct in their conclusions. I recall having made careful investigations of patients with idiopathic epilepsy on a standardized regimen, studying the acid-base equilibrium, the degree of ketonuria and the water and electrolyte balances before and after giving them ketogenic diets. I observed that when the patient was well under control on the ketogenic diet, convulsions could be induced again by increasing the total diet without change in the ketogenic to antiketogenic ratio. Although such patients received more fat and, therefore, more glycerin, they lost their ketosis and had recurrence of seizures. Under such conditions, increasing the food resulted in a shunting of fat into the depots of the body, while the extra carbohydrate and protein were used as antiketogenic substances. Obviously, the mechanism by which glycerin acts would not be the same in those studies and in these reported by Dr. Kajdi and Dr. Livingston. I should like to know more exactly the composition of the diets in these cases, because, a severely epileptic patient who responds well while on a strongly ketogenic diet will have seizures again on administration of 50 Gm. of glucose. Would glycerin have the same effect merely by acting as an antiketogenic agent or would it serve as a reenforcement to the anticonvulsant action of the ketogenic diet?

Mumps Meningoencephalitis With and Without Parotitis. DR. LAWRENCE KILHAM, Boston.

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DISCUSSION

DR. T. F. MCNAIR SCOTT, Philadelphia: I think Dr. Kilham has done a service in emphasizing the frequency of mumps as a cause of meningoencephalitis. My associates and I in Philadelphia, during the last two years, have studied 180, in round figures, cases of meningoencephalitis, and, of these, 52 were shown to be mumps and 11 were shown to be lymphocytic meningitis; the remainder, about 60 per cent, were undiagnosed by laboratory means. Did Dr. Kilham get the

spinal fluids freshly from the hospital; did he take any precautions in getting them? Has he considered the taking of such precautions to be a factor in his ability to isolate the virus from the spinal fluid?

DR. ALBERT B. SABIN, Cincinnati: Dr. Kilham has contributed greatly to our understanding of the viral infections of the nervous system by his studies on mumps, and I think that it is important for us to know the proportion of the large number of so-called aseptic cases of meningitis that may be due to the virus of mumps during different seasons of the year. Both Dr. Kilham and Dr. Scott have reported finding a high incidence of meningitis due to mumps, and I wonder whether their results may not perhaps be exceptional. It is important to remember one phrase in Dr. Kilham's report, that his studies were made during a year of exceptionally high incidence of mumps.

Some of you may be familiar with the report from the Army Medical School on a study carried out over a period of years in which an attempt was made to find an etiologic basis for the cases of aseptic meningitis encountered in the Army. There mumps meningitis, together with lymphocytic choriomeningitis and herpes simplex accounted for about 25 per cent of the total incidence. That still left about 75 per cent of the cases of aseptic meningitis without an established causation, most, if not all, probably due to the virus of poliomyelitis.

In 1946, many cases of "aseptic meningitis" occurred among American troops in Japan, who were mostly young men 18 to 21 years of age. I carried out a similar study; in only 2 of the 20 patients who were studied was mumps found to be the etiologic agent, and these 2 apparently acquired their infection during an outbreak of mumps aboard ship. In other patients, poliomyelitis virus was recovered from the stools.

I think it is important to utilize the diagnostic methods which, as Dr. Kilham has indicated, are now more readily available, to determine how large a proportion of the cases of aseptic meningitis during the summer are actually due to mumps, particularly during years when mumps is not prevalent in the spring. You may recall Dr. Charles Armstrong's important observation (*Tr. & Stud., Coll. Physicians, Philadelphia* **8**:6, 1940) that lymphocytic choriomeningitis rarely occurs during the months of the year when poliomyelitis is most prevalent. It would be worth knowing the extent to which this may also be true of mumps meningitis unassociated with parotitis.

DR. LAWRENCE KILHAM, Boston: In regard to Dr. Scott's question about the isolation of the mumps virus, I was not too concerned if the samples were at room temperature for more than a few hours. It was never any longer than that before the material was put into the eggs.

Treatment of Tuberculous Meningitis with Streptomycin and Promizole.®

DR. EDITH M. LINCOLN, New York.

In the children's chest clinic of Bellevue Hospital, all patients with tuberculous meningitis have been treated with streptomycin and a sulfone, promizole® (4,2′-diaminophenyl-5′-thiazolesulfone). Chemotherapy with promizole® was begun in 1944. The sulfone used alone had no effect in the treatment of tuberculous meningitis. However, 5 of 7 consecutive patients with miliary tuberculosis treated with promizole® have survived two and a half to almost five years and are free from evidence of the disease. Promizole® is a slowly acting drug but it has the advantage of producing relatively little toxicity; it is administered by mouth and can be given over long periods safely and effectively. Streptomycin is the most valuable tuberculostatic agent known; it is toxic especially for the vestibular branch

of the eighth nerve and its use for more than short periods causes the emergence of resistant tubercle bacilli. We decided to combine these drugs in the treatment of meningitis, hoping to utilize the rapid action of streptomycin and the long range bacteriostatic action of promizole.® Moreover, we hoped to get a therapeutic result greater than was to be expected from the additive effect of the two drugs. Most important of all, we hoped by using two different types of drugs to diminish or delay the emergence of resistant organisms.

Up to the present, we have treated 19 children with tuberculous meningitis. Each child received 1 Gm. of streptomycin daily by the intramuscular route for a period of six months. Forty intrathecal injections of streptomycin were given, ranging from 0.05 to 0.1 Gm. Enough promizole® was given orally to maintain a blood level of 1 to 3 mg. per hundred cubic centimeters. Five children have died. Only 1 of the survivors has not yet completed the initial six months' course of combined therapy with streptomycin and promizole.® The 13 others have been followed from six to twenty-four months. All the survivors behave normally and none has serious neurologic damage. Three have had relapses; organisms fully sensitive to streptomycin were recovered from the spinal fluid early in the course of relapse.

Our convalescent children are presenting many new problems, and we are developing a rehabilitation program which includes the services of teachers and recreational workers, as well as of an orthopedist, psychiatrist and physical therapist.

DISCUSSION

Dr. Herbert C. Miller, Kansas City, Kan.: How did Dr. Lincoln arrive at a period of six months for treatment? It seems to me that some relapses occurred at the end of six months. Were some of the children that were treated for the six months' period completely well; did she keep up the treatment in spite of the fact that they seemed completely well? Was the protein content of the spinal fluid, and other factors of that kind, of any help to her in deciding to terminate the treatment after six months?

Dr. Arild E. Hansen, Galveston, Texas: My associates and I feel ourselves chastened because we have not followed through with this same idea. We, too, were planning to use promizole® in addition to streptomycin in the treatment of tuberculous cases of this type but were influenced by Dr. Lars Söderhjelm, a Swedish physician who joined our group, to try paraaminosalicylic acid in combination with streptomycin. He reported excellent results with this combination. I am sorry to state no favorable effects were observed in a series of 6 cases with this combined therapy.

Dr. William Berenberg, Boston: My associates and I have treated 38 patients with tuberculous meningitis. The first 20 patients received only streptomycin. The results over an extended period of time were universally poor, as most investigators have found. More recently, we treated 18 infants and children with streptomycin plus paraaminosalicylic acid. In addition, alternate children received promizole.® Our results in the patients receiving promizole® have not been as promising as those reported by Dr. Lincoln. Most of our patients had been ill with meningeal symptoms for a considerable time before they arrived at the hospital. It is my feeling that the duration of the disease before the onset of therapy is of extreme prognostic importance in this form, as well as in other forms, of meningitis. I should like to ask Dr. Lincoln how long her patients, in general, had been ill before therapy was instituted.

DR. LAWSON WILKINS, Baltimore: I was interested in the sexual precocity reported in the patients with miliary tuberculosis who had recovered after promizole® therapy. Dr. Lincoln, was there evidence of any hypothalamic lesion such as diabetes insipidus which would suggest that perhaps a healed miliary tubercle in the brain centers brings about sexual precocity. It is well known that sexual precocity may develop after measles encephalitis and other types of encephalitis affecting the hypothalamus.

DR. EDITH M. LINCOLN, New York: A period of six months for treatment, of course, was arrived at more or less arbitrarily. There were no standards for the length of time one should treat a child with streptomycin. We followed largely the period of time which the workers for the Veterans Administration, who had been treating patients long before we started, were using. However, we did lengthen the period for administration of streptomycin from four to six months.

The protein tended to be normal at the close of treatment in all our patients except 4, and 2 of those did have relapse. Sugar levels were normal and the clinical condition was entirely satisfactory in all the patients.

We believe, also, that since six months is an arbitrary period it is obvious that we should have gone on treating those children with relapses for a few months more; except for the lead that the high protein level gives us, so far we have no way of knowing which children are going to relapse.

Another aid, however, which the British workers first pointed out and which we have been using, is the increase in the streptomycin level of the spinal fluid at the beginning of relapse. As is well known, there is practically no streptomycin in the fluid on intramuscular therapy unless there is meningitis. In 2 of our patients, we were warned of relapse by a rise in the streptomycin level of the spinal fluid. Dr. Berenberg may be right in that, in general, the condition in our patients was of shorter duration before treatment; I think that may explain, in part, the fact that we had fewer mental sequelae. All the cases of meningitis were from our own service, so that we probably did diagnose the condition and start treatment earlier than we would have if the patients were sent in.

On the other hand, animal experimentation has given us no reason to believe that the duration of disease before the onset of therapy is of value in the prognosis. Smith, Emmart and McClosky *(Am. Rev. Tuberc.* **58**:112, 1948) concluded that the duration of treatment is more important than the interval between infection and the beginning of treatment.

In the children who acquired secondary sex characteristics during treatment by promizole,® we had no evidence of hypothalamic lesions. In fact, we have no adequate explanation for their development of these lesions. We have seen no such reaction in boys, only in girls.

Cardioesophageal Relaxation as a Cause of Vomiting in Infants. DR. WILLIAM BERENBERG and DR. EDWARD B. D. NEUHAUSER, Boston.

Recurrent vomiting in the young infant may be due to a wide variety of causes. During a five year period of study among this group, 24 patients have been observed and followed in whom the dysfunction was produced by a relaxation of the portion of the esophagus at the hiatus, with failure of the normal "sphincter" action of the cardia. Because the condition appeared to be the opposite of achalasia or cardiospasm, it has been termed "chalasia."

It appears likely that this syndrome is produced by an autonomic imbalance with either vagal stimulation or sympathetic inhibition. Other less likely anatomic

or physiologic abnormalities might also play an etiologic role. Persistent vomiting usually starts within the first week of life and becomes progressively worse. It is most apt to occur when air is expelled or when the patient is supine. Physical examination and other studies are invariably unrevealing. Fluoroscopic examination of the swallowing function with barium sulfate reveals persistent failure of the "pinchcock" action of the cardia. During inspiration, the esophagus dilates and fills with barium sulfate from the stomach. During expiration, the filled esophagus is compressed. With the patient supine, retrograde filling of the esophagus may be produced by an increase in intra-abdominal pressure.

All patients have responded well to an empiric regimen under which they are given thickened feedings and kept in an erect position for a prolonged period thereafter. Repeat fluoroscopic examination some months later usually reveals no abnormality.

DISCUSSION

DR. JOHN CAFFEY, New York: My associates and I looked carefully for relaxation of the esophagus in vomiting infants since the first report by Neuhauser and Berenberg in 1947. So far, we have not detected the disorder in a single patient. Perhaps we are not using the same criteria for diagnosis. I should appreciate learning from Dr. Berenberg more about exact requisites for a conclusive diagnosis, especially the consistency of the findings in the same patient from day to day. Regurgitation of mixtures of barium sulfate and water and gas from the stomach into the esophagus, sometimes in large amounts, is, of course, common in the large majority of all infants who swallow barium sulfate. However, we have not yet encountered an infant in whom retrograde flow from the stomach into the esophagus could be induced consistently by manual pressure on the stomach or by placing the infant in the recumbent position.

Vomiting due to cardioesophageal relaxation is said to be lessened by maintaining the infant in the erect position during and after feeding. This finding should not be used as a pathognomonic sign of cardioesophageal relaxation because similar improvement occurs in infants maintained in the erect position who vomit owing to swallowing of air when they are fed.

DR. FREDERIC SILVERMAN, Cincinnati: My colleagues and I have observed one such patient in Cincinnati within the past year and a half, a child 3½ or 4 months of age who had a history of considerable feeding difficulty. The condition was first observed on fluoroscopy; I should like to emphasize Dr. Berenberg's statement concerning fluoroscopy. It is so trite and so simple that we often overlook the fact that a roentgenogram is an instantaneous exposure of a system which can vary from time to time. In any event, our infant improved appreciably with respect to the regurgitation after being held in the erect position for some time. Subsequently, intensive psychotherapy was introduced in an effort to improve the patient-mother relationship, and at last reports the child was doing well.

DR. WILLIAM BERENBERG, Boston: Our feeling at one time was exactly that of Dr. Caffey. We wondered whether this condition represented a real entity or only a temporary phenomenon to be seen one day and not the next. However, in repeated fluoroscopic studies on the same child, we were able to demonstrate the same abnormality over and over again. Since this symptom complex was first described, we have received numerous communications from roentgenologists who have been able to demonstrate persistent cardioesophageal relaxation in infants with repeated vomiting. Dr. Elaine Field has now recognized typical examples of chalasia in a significant number of infants at The Great Ormond Street Hospital,

in London, England. It is our feeling that we have described a clinical syndrome and not necessarily a specific disease. This conclusion seems amply justified by virtue of the characteristic symptomatology, the roentgenologic appearance and the constant response to specific, although empiric, therapy.

Poisoning Due to Excess Vitamin A; Its Relation to Infantile Cortical Hyperostosis. Dr. John Caffey, New York.

The clinical, roentgenologic and chemical findings in 4 infants who had poisoning due to ingestion of large amounts of percomorph liver oil are presented. The long incubation period of approximately six months is emphasized, as well as the rapid subsidence of the clinical manifestations after withdrawal of percomorph liver oil.

The similarities and differences between poisoning due to vitamin A and infantile cortical hyperostosis are discussed. The absence of mandibular and scapular involvement, the later onset, the dramatic relief of symptoms after a few days' withdrawal of all types of vitamin A preparations and the history of chronic ingestion of vitamin A are the principal features of vitamin A poisoning which differentiate it from true infantile cortical hyperostosis. The similarity of the soft tissue swellings and roentgenologic findings in the skeleton in the two conditions is stressed. The question is raised whether a preparation potentially as dangerous as percomorph liver oil and other vitamin A concentrates should be marketed without more precautions than are used at present.

DISCUSSION

Dr. Hugh W. Josephs, Baltimore: Since my first report (Hypervitaminosis A and Carotenemia, Am. J. Dis. Child. **67**:33-43 [Jan.] 1944) in 1944, I have had 4 more cases, 1 of which was sent in from outside. I want to show slides on these to you now. The picture may fill in some of the gaps. Clinically speaking, I have nothing much to add to what Dr. Caffey said. The importance of recognizing the condition, I think, is great. The condition may be much commoner than we have any idea of at present. [Slides]

Dr. J. M. Lewis, New York: It seems to me that there are more cases of hypervitaminosis A than there are instances of frank vitamin A deficiency, if we exclude those cases of vitamin A deficiency complicating diseases in which an interference exists with the absorption of the vitamin as, for example, cystic fibrosis of the pancreas and celiac disease. In other words, the danger of hypervitaminosis A appears to be greater than the possibility of development of vitamin A deficiency among normal infants and children. We have maintained through the years that supplementation of the diet with vitamin A products is superfluous for normal infants and children except in unusual circumstances when the child vomits frequently or refuses the major portion of its diet. Of course, children with steatorrhea and premature infants should receive vitamin A supplements, preferably in the aqueous preparations.

Most of the cases hypervitaminosis A have resulted from long-continued use of excessive doses (1 to 2 teaspoonfuls [8 to 10 cc.]) of a highly potent preparation (50,000 to 60,000 units of vitamin A per cubic centimeter). The possibility of vitamin A poisoning would be much more remote if the concentration of vitamin A in all preparations were standardized to 5,000 or 10,000 units per cubic centimeter. Furthermore, the size of the bottles should be restricted to a capacity of 10 or 15 cc. rather than 50 cc., as overzealous mothers would be less likely to give 1 to 2

teaspoons of a vitamin A preparation when the capacity of the bottle is only 10 to 15 cc. I think that, eventually, manufacturers will be required to meet regulations of this type.

DR. JOHN CAFFEY, New York: Dr. Josephs, none of these patients showed accelerated skeletal development. In experimental vitamin A poisoning with small animals, Wolbach found all features of bone growth accelerated, especially tubulation. I am in complete agreement with Dr. Lewis. There is no good reason a healthy infant or child taking a normal formula or diet should receive added concentrate of vitamin A. These preparations are needless, expensive and potentially dangerous in the hands of mothers for daily administration to healthy infants and children.

Hyaline-like Material in the Lungs of Newborn Infants: Its Incidence, Pathogenesis and Role in Fetal and Neonatal Mortality. DR. HERBERT C. MILLER and DR. M. HARRY JENNISON, Kansas City, Kan.

Evidence has been presented in an earlier study by Miller and Hamilton indicating that the "vernix membrane" in the lungs of newborn infants probably is the result of an injury to the epithelium lining the bronchioles, alveolar ducts and terminal air spaces and does not result from aspiration of the contents of the amniotic sac. The nature of the injury postulated in the investigation referred to was not determined, although the lesion in the lung of the newborn infant resembled those seen in older persons who died from pandemic influenza, acute pneumonias of coccic origin and rheumatic pneumonitis.

In the present study an investigation was made on 4,117 consecutive births to determine what, if any, clinical factors might help explain the pathogenesis of this pulmonary lesion. There were 66 fetal and 85 neonatal deaths among the 4,117 births; 28 of the 85 infants had lesions in their lungs.

Based on the postmortem examination of 71 of the 85 infants who died during the neonatal period, 27.5 per cent of all liveborn infants who weighed from 1,001 to 1,500 Gm. at birth had this hyaline material in their lungs, often in the form of a membrane. The incidence diminished to 11.1 per cent among infants weighing 1,501 to 2,000 Gm. and continued to decrease, so that in infants weighing more than 3,000 Gm. it was practical nonexistent. The lesion was also practically nonexistent among infants weighing less than 1,000 Gm. It rarely occurred in the lungs of stillborn infants. The pattern of distribution was the same in both white and nonwhite infants in the various weight groups.

The pulmonary lesion was more apt to be found among infants whose mothers had no serious complications of pregnancy and labor than among those whose mothers did. The lesion occurred less frequently among infants with some obvious clinical or anatomic explanation for their deaths than it did among infants who had none. These were significant differences.

If a liveborn infant in this series weighing over 1,000 Gm. at birth died during the first twenty-four or forty-eight hours of life and came to autopsy, there was a 65 per cent chance that the pulmonary lesion would be observed. The chances of observing the lesion at autopsy was increased to 90 per cent if there was no obvious clinical explanation for the baby's death and no serious maternal complication of labor or pregnancy. It was felt that the lesion was the sole cause of death in 11 of the 71 infants who had postmortem examinations and that it shared equally with other causes in 11 additional cases. The sex, order of birth, length of labor, the time that elapsed between rupture of the membranes and delivery,

the method of delivery, the mother's age and the feeding or withholding of food appeared to have no relation to the occurnence of the lesion. The causation of the lesion was discussed in the light of these observations.

Analysis of the 85 neonatal deaths indicates that the primary cause of death was ascertained in about 80 per cent of all infants weighing more than 1,000 Gm. at birth. The higher mortality among premature infants was related to the fact that certain disease conditions were more apt to occur in these infants, such as the presence of hyaline-like material in the lungs, cerebral hemorrhage and infections, rather than to the fact they were merely premature.

DISCUSSION

Dr. James L. Wilson, Ann Arbor, Mich.: Ten or twelve years ago, Dr. Sidney Farber and I were attempting to study the pathogenesis of atelectasis in the newborn and, incidentally, became interested in this so-called hyaline membrane. We did not collect anything such as the statistical incidence that Dr. Miller has reported, but we did attempt to produce, experimentally, and with some success—as far as I can tell with my histologically uneducated eye—findings that are similar to Dr. Miller's membranes.

We did it in two ways, by suspending the dead lungs of the autopsied infant in a small respirator, giving it artificial respiration and, at the same time, injecting into the trachea different materials; the ones which most closely produced this was ordinary human serum. We also injected subcutaneously serum and air into some of the dead infants' skin and were able to produce outside the lung the same phenomena.

It seems to us, therefore, that this hyaline membrane in the newborn which had been described for years as caused by influenza and such diseases was really an accidental finding, and that it was a function of two factors, the outpouring of serum into the lungs and agonal dyspnea.

Dr. Herbert C. Miller, Kansas City, Kan.: Dr. Wilson, I recall your studies, because I pored over them. One of the things that you were not able to do in your study was to demonstrate fat in any of the membranes you produced in animals. Since fat is present in the membranes found in some babies' lungs, it would seem essential to demonstrate it in the experimental animal. Unless this can be done, I do not believe we are justified in believing that the experimentally produced membranes are comparable to those seen in the lungs of newborn infants. The point is further complicated because fat has not been demonstrable in all the lungs of newborn infants containing hyaline membranes. Our understanding of the composition of these hyaline membranes would be clearer if we knew the reason fat was present in some membranes and not in others and the source from which it was derived.

Glycogen Disease. Dr. L. Emmett Holt Jr. and Dr. Murray H. Bass, New York, and Dr. Sampson J. Wilson, Brooklyn.

Two instances of glycogenosis (von Gierke's disease) were observed in infants in whom fasting, induced for the sake of studying the curve for sugar tolerance, precipitated pronounced hypoglycemia and collapse, from which the patients could not be rallied by intensive administration of glucose. It is noteworthy that ketosis was absent in both of these infants, and that the liver was fatty in addition to presenting the typical picture of glycogen disease. The interpretation drawn is that (1) these infants were unable to respond to hypoglycemia by burning fat and (2)

there was a defect in carbohydrate combustion, in addition to the well known defect in glycogenolysis. Some support for these concepts is obtained from a study of the literature. The need for caution in studying these cases is emphasized.

DISCUSSION

Dr. James L. Wilson, Ann Arbor, Mich.: I have been caring for a patient with this disease for the last two years. He came to our attention because of severe repeated convulsions. The mother was an excellent trained nurse and learned that she could stop the convulsions by giving him carbohydrate. We had him in the hospital when I was interested in making curves for amino acid absorption in this complex disease. Just before we started one test, we were quite certain he was going to have a convulsion. He had the incident shock picture. We gave him gelatin in the usual way, and he immediately improved.

A blood sugar curve which we made, giving the values for gelatin instead of sugar, showed a definite but small rise. We gave him a diet low in carbohydrate and high in protein, which he took satisfactorily, and over the course of a year and a half he has had no convulsions and has grown. He still has the glycogen disease, unfortunately, though he has shown little urinary acetone.

Dr. Irving J. Wolman, Philadelphia: These cases are rare and always excite interest when they appear. I have had a chance to study 2 cases in the same family. Several similar families in which more than one instance has occurred are on record; this confirms the impression that the defect is a congenital disturbance. Many of the patients also have had a pronounced lipemia, which probably is related to the fatty liver so often present.

Dr. L. Emmett Holt Jr., New York: I should like to agree with what Dr. Wilson has said—that protein is highly effective in the treatment of the disease. It furnishes an indirect source of sugar, protecting the patient from hypoglycemic attacks better than any other form of diet. The coexistence of lipemia and a fatty liver with glycogen disease appears to be the rule rather than the exception in young infants. Lipemia was observed in one of our reported patients, but measurements were not made in the other. There is evidence that the abnormality in fat metabolism is outgrown. A patient of Dr. J. B. Sidbury, Wilmington, N. C., who was subsequently studied by Dr. E. M. Bridge, of Buffalo, and myself, had a severe lipemia at the age of 2 years which had disappeared by 6 years of age. We have observed another instance at Bellevue Hospital in which a patient with glycogenosis as an infant exhibited lipemia which subsequently disappeared.

Even the abnormality of carbohydrate metabolism tends to improve to some extent with time. There are six or seven reports in the literature testifying to this point. Dr. Sidbury tells me that the patient we studied some years ago is now 15 years of age and that his liver is now virtually normal in size; attacks of hypoglycemia have disappeared, and the blood sugar, when measured, has not been below normal limits.

CORRECTION

In the January 1950 issue of the American Journal of Diseases of Children, in the article "Cystic Change in the Pancreas: Its Experimental Production," by Peter V. Véghelyi, M.D.; Tibor Kemény, Drd.M., and Joseph Sós, M.D., both photomicrographs in figure 3, page 67, are of the pancreas of a rat killed on the sixty-fifth day of the experiment.

Book Reviews

Pediatric Anesthesia. By Morton Digby Leigh, M.D., and M. Kathleen Belton, M.D. Price, $5.50. Pp. 240, with 84 illustrations. The Macmillan Company, 60 5th Ave., New York 11, 1948.

The need for a treatise on pediatric anesthesia has long been recognized by those interested in surgical and medical pediatrics. This first book on pediatric anesthesia is in no sense theoretic or highly technical, but it is a well organized practical essay based on the wide experiences of the authors.

Leigh and Belton stress the psychologic, anatomic and physiologic differences between infants and adults. The introduction, dealing with the psychologic approach to children, is far more important than the few pages would indicate. However, this attention to the mental comfort of the patient is reemphasized throughout the book.

The first chapter deals with the preoperative preparation which is much too frequently neglected in infants and children. The need of preoperative sedation is stressed. Several dosage tables are given for sedative and pain-relieving drugs. The suggested doses are wisely ultraconservative, as the administration of any sedative to infants may seem a radical measure to many pediatricians and pediatric surgeons.

The chapter on respiration and circulation emphasizes the differences between the physiologic makeup of the infant and that of the adult. The authors point out that more than 99 per cent of the anesthetic fatalities are due to some interference in one or the other of these two systems. This chapter is truly fundamental and forms the basis of all good anesthesic practice.

Modifications of technics for adults which the authors have used with success are discussed in the chapters on inhalation, rectal, intravenous and local administration of anesthesia. Intubation and the choice of agent and technic are dealt with in separate chapters.

Although anesthetic complications are discussed more or less throughout the book, a separate chapter on complications, many of which are peculiar to children, reemphasizes the importance of prevention, early recognition and treatment of these conditions. Chapters on postoperative care, oxygen therapy and fluid therapy suggest that the responsibility of the anesthesiologist does not end at the termination of the operation.

The book is interestingly written and profusely illustrated. It will be a valuable addition to the library of any pediatrician or anesthesiologist interested in pediatric anesthesia.

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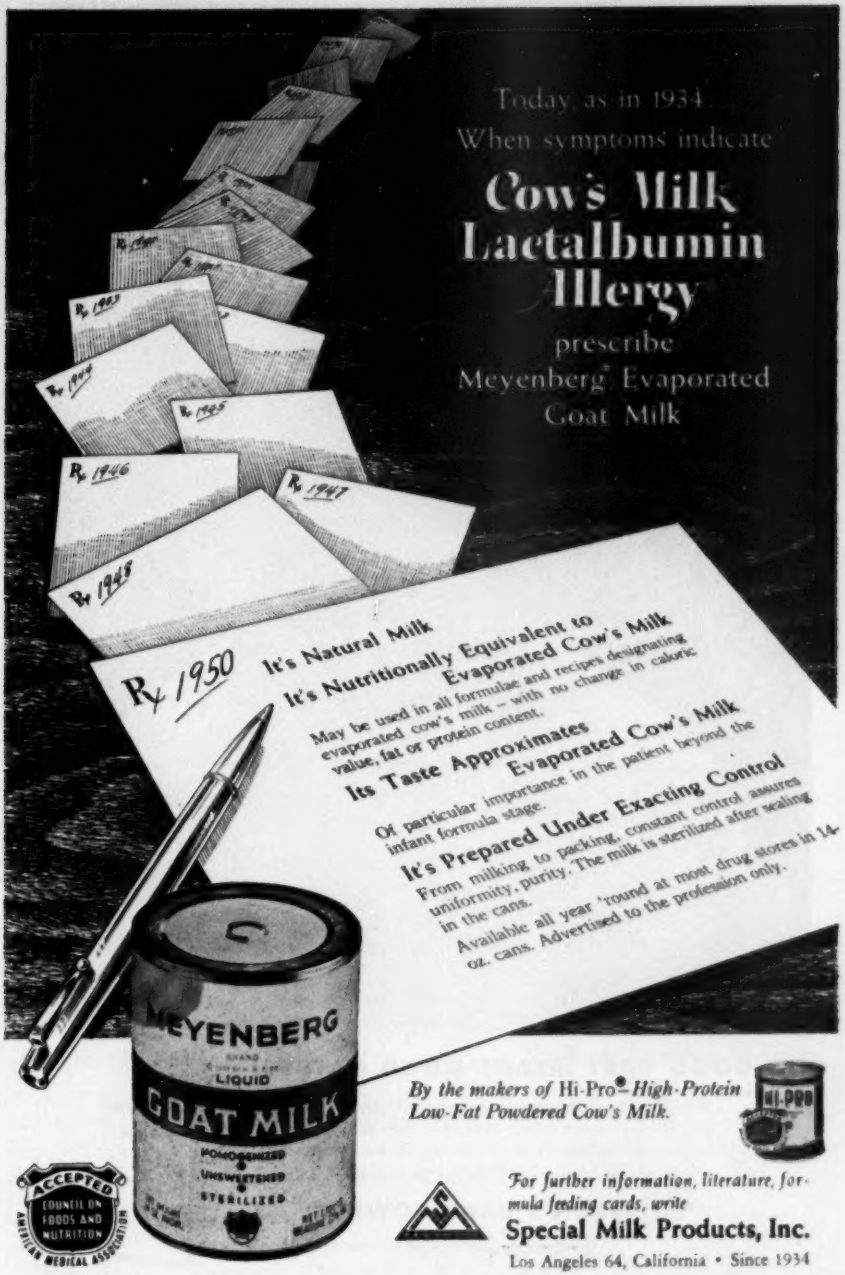
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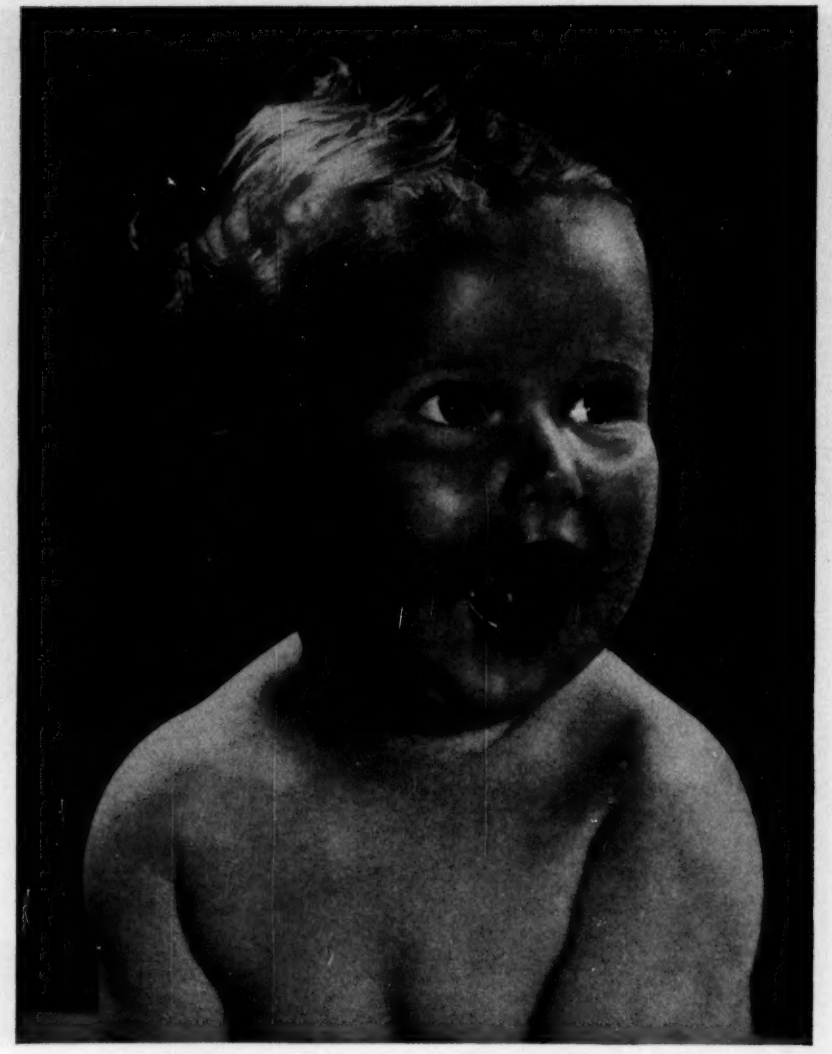

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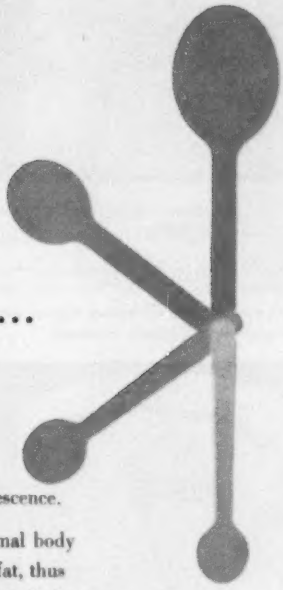

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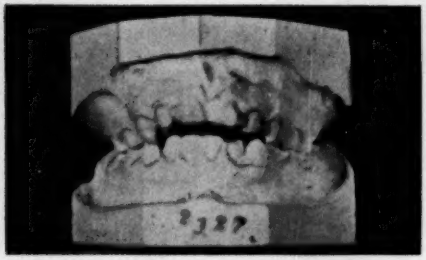

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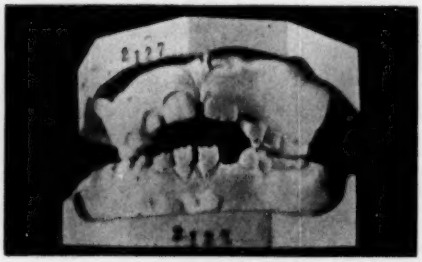

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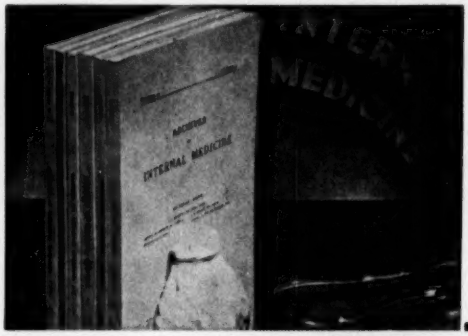

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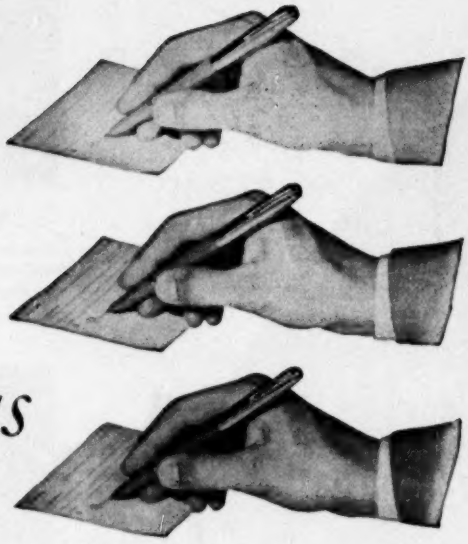

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